COGNITIVE DYSFUNCTION IN OLDER BREAST CANCER SURVIVORS

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Adele Deborah Lenae Crouch

COGNITIVE DYSFUNCTION IN OLDER BREAST CANCER SURVIVORS

Up to 75% of the more than 3.5 million breast cancer survivors (BCS) living in the United States report cognitive dysfunction. However, little is known about cognitive dysfunction among older BCS, who may be at greater risk. Therefore, the purpose of this dissertation was to characterize cognitive dysfunction in older BCS. Specific aims included:

(1) synthesize the literature regarding cognitive dysfunction in older BCS; and

(2) examine the relationships between a) objective cognitive function (immediate memory, delayed memory, attention, executive function-working memory, verbal fluency) and subjective cognitive function (attention); b) demographic factors, medical factors, treatment factors, and cancer-related symptoms (depressive symptoms, anxiety, fatigue, sleep disturbance) and cognitive function; and c) comorbidity and cognitive function and physical functioning, and quality of life (QoL) in older BCS.

In an integrative review, to address aim 1, 12 studies were identified. Up to 41% of older BCS showed objective cognitive dysfunction on neuropsychological assessment, up to 64% reported subjective cognitive dysfunction concerns pre-treatment, and 50% incurred cognitive decline from pre- to post-treatment. Cognitive dysfunction was associated with older age, multiple comorbidities, chemotherapy, sleep disturbance, neuropsychological symptom cluster, frailty, and poorer QoL.

To address aim 2, data were leveraged from a large, nationwide, QoL in younger versus older BCS study (PI: Champion), which included 335 older BCS who were ≥60 years of age, had breast cancer (stage I-IIIa), received chemotherapy, and were 3-8 years

post-diagnosis without recurrence. Findings included up to 19% of older BCS had mild-moderate objective cognitive dysfunction on at least one neuropsychological assessment, with 26% reporting poor-moderate subjective attention function. BCS, who were older, had less education and more depressive symptoms had greater cognitive dysfunction. Objective attention and executive function-working memory significantly and positively correlated with subjective attention. In turn, subjective cognitive dysfunction and increased number of comorbidities were related to poorer physical functioning. Subjective cognitive dysfunction was also related to poorer QoL. The findings from this study highlights the prevalence and complexity of cognitive dysfunction in older BCS. Further research is needed to better understand the intersection of aging, cancer, comorbidities and cognitive dysfunction and the negative implications in older BCS.

Diane Von Ah, PhD, RN, FAAN, Chair

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LIST OF ABBREVIATIONS

BCS	Breast Cancer Survivor
QoL	Quality of Life
IU	Indiana University
ECOG	Eastern Cooperative Oncology Group
IRB	Institutional Review Board
NCC	Non-Cancer Control
SD	Standard Deviation
CESD	Center for Epidemiologic Studies Depression
STAI	State-Trait Anxiety Inventory
FACT-F	Functional Assessment of Cancer Therapy: Fatigue
PSQI	Pittsburg Sleep Quality Index
AVLT	Rey Auditory-Verbal Learning Test
WAIS	Wechsler Adult Intelligence Scale
COWA	Controlled Oral Word Association
AFI	Attentional Function Index

CHAPTER 1

Background and Significance

Breast cancer survivors (BCS) make up the largest group of cancer survivors with approximately 3.5 million BCS living in the United States alone [1]. Of those BCS, over 60% are 60 years of age and older and that number is expected to grow as society continues to age [2-7]. Advances have been made in detection, earlier diagnosis, and improved treatment of breast cancer including precision health and targeted therapeutics, which has contributed to increased long-term survival [2]. In fact, breast cancer mortality rates have decreased steadily and rapidly from 1989 to 2015 with a total decrease of 39% [1]. Relative survival rates have increased and are now at 91% at 5-years after diagnosis, 86% after 10-years, and 80% after 15-years [1]. As the expected survival from breast cancer lengthens and age expectancy of the nation's population increases, older BCS (≥60 years of age) represent the largest population in the cancer survivor community [5]. BCS incur a myriad of physical, psychological, social, and cognitive symptoms resulting from their breast cancer diagnosis and treatment that can persist into survivorship [8].

One symptom BCS may incur after cancer diagnosis and treatment is cognitive dysfunction. Cognitive dysfunction includes both objective cognitive dysfunction measured by performance on neuropsychological assessments and subjective cognitive dysfunction or self-reported concerns by BCS. Cognitive dysfunction is a prevalent, bothersome, and potentially debilitating problem for many BCS following chemotherapy treatment. Research has shown that up to 75% of all age BCS report cognitive dysfunction, including concerns of forgetfulness or recalling information, problems with processing information and multi-tasking, and/or difficulties problem-solving after cancer

treatment [1,2,4,9-12]. Meta-analyses also support the prevalence of objective cognitive dysfunction, including primarily deficits in memory, speed of processing, and executive function in all age BCS [13,14]. However, none of the published meta-analyses and very limited studies to date have focused on older BCS. With the aging population and increased survival rates, more research is needed to understand and characterize both objective and subjective cognitive dysfunction in older BCS, the largest cancer survivor group [2].

Older BCS may be at a greater risk of suffering from cognitive dysfunction after breast cancer diagnosis and treatment with chemotherapy. Older BCS were defined as women who were diagnosed with breast cancer and who were 60 years of age and older at the time of diagnosis. This definition coincides with the definition used in the Older Americans Act and the Centers for Disease Control report for identifying vulnerable older adults [15]. Focusing on older BCS in this age group is important because they make up the majority of new breast cancer cases, are the largest sub-population of BCS, and older BCS are believed to be more susceptible to cognitive dysfunction [16,17].

Older BCS may be at an increased risk for cognitive dysfunction after breast cancer diagnosis and treatment due to a number of factors, including the normal aging process, pre-existing conditions or comorbidities, the neurotoxic effects of chemotherapy treatments and/or a combination of these factors [3,15-24]. Normal aging is often associated with some cognitive decline and thus, older BCS may have lower baseline cognitive reserve prior to chemotherapy treatment, placing them at greater risk for cognitive dysfunction. In fact, a study by Ahles and colleagues (2010) demonstrated that older age, chemotherapy exposure, and lower cognitive reserve are associated with

increased cognitive dysfunction among a group of all age BCS [3,25]. Chemotherapy has also been shown to have neurotoxic effects. Researchers have established that BCS who received chemotherapy may have both structural (white and gray matter changes) and functional changes, which have been related to both objective and subjective cognitive dysfunction in the literature [26-29]. In fact, chemotherapy has been hypothesized as accelerating the effects of aging, as both are associated with similar biologic changes including DNA damage, oxidative stress, inflammation, and shortened telomere length [3,30,31]. This accelerated aging process, in turn, may hasten cognitive decline in some BCS, especially older BCS [3]. Thus, older BCS who receive chemotherapy may be at an increased risk for cognitive dysfunction; however, more research is needed to address this at risk population [3].

Despite the fact that cognitive dysfunction is receiving more attention, researchers have continued to focus on all age BCS. Less is known about cognitive dysfunction among older BCS (women diagnosed with breast cancer who are 60 years of age and older). Most of the research regarding cognitive dysfunction has been conducted with all age BCS. Thus, there is a need to both conduct a thorough review of this literature and conduct more research to fully characterize cognitive dysfunction in older BCS in order to develop interventions.

The existing literature regarding cognitive dysfunction in BCS has been limited by varying definitions and measures of cognitive dysfunction, with most studies failing to include measures of both objective and subjective cognitive function. Although, objective cognitive assessments have been identified as the ‘gold standard,’ subjective or self-reported cognitive concerns are often the first indication of cognitive dysfunction and

have been hypothesized to represent more subtle changes following treatment [10,32,33]. Therefore, it is essential to measure both to fully characterize cognitive dysfunction, as well as, to determine if these measures are associated.

It is also critical to elucidate factors that characterize older BCS with cognitive dysfunction so evidence-based interventions can be developed to improve cognitive dysfunction, and ultimately improve quality of life (QoL). Research has shown that demographic factors (age and education), medical factors (comorbidities), and treatment factors (time since diagnosis and breast cancer stage) may be related to cognitive dysfunction; however, research has been mixed [23,24,34]. Cancer-related symptoms (depressive symptoms, anxiety, fatigue, and sleep disturbance) have also been prominently reported and linked to cognitive dysfunction in all age BCS; [35-38] however, only a few studies have examined this relationship in older BCS, and results have been equivocal [23,24,39].

Cognitive dysfunction may also be related to decreased physical functioning and QoL, which is important to understand, especially in older BCS [23,34,39-43]. The paucity of research regarding cognitive dysfunction in older BCS demonstrates a significant gap in knowledge and with the rapidly aging population represents a significant challenge in providing quality cancer care in the future [44-49].

Purpose, Specific Aims, and Research Questions

Overall, the purpose of this dissertation study was to fully characterize cognitive dysfunction in older (≥60 years old) BCS. Specific aims are to:

Aim 1: Synthesize the literature regarding cognitive dysfunction in older BCS.

Specifically, examine the prevalence of cognitive dysfunction in older BCS,

including both objective and subjective measures and examine factors associated with these measures of cognitive dysfunction.

Aim 2: Examine the relationships:

a) between objective cognitive function (immediate and delayed memory, attention, executive function-working memory, and verbal fluency) and subjective cognitive function (subjective attention);
b) between demographic, medical, treatment factors, and cancer-related symptoms (depressive symptoms, anxiety, fatigue, and sleep disturbance) and objective cognitive function and subjective cognitive function; and
c) between comorbidities, objective cognitive function, and subjective cognitive function and physical functioning and QoL, in older BCS.

This dissertation will address the following research questions illustrated in Figure 1-1 including: (1) What do we currently know regarding cognitive dysfunction among older BCS? (2) Are there relationships between objective measures and subjective measure of cognitive function among older BCS? (3) Are demographic factors, medical factors, treatment factors, and cancer-related symptoms related to objective and subjective cognitive function among older BCS? (4) Are comorbidities and objective and subjective cognitive function related to physical functioning and QoL among older BCS?

Conceptual Framework

The guiding conceptual framework for this study, which is congruent with the parent study, was derived and modified from Hess and Insel's (2007) Conceptual Model of Cancer-Related Changes in Cognitive Function and from the relevant literature (see Figure 1-1) [50]. The model examines the physiologic and psychological factors

(antecedents and consequences) related to cancer-related changes in cognitive function and provides a rational framework. The model depicts that certain demographic, medical, and treatment factors, and cancer-related symptoms are linked with cognitive dysfunction and that cognitive dysfunction following cancer diagnosis and treatment is related to untoward outcomes or consequences including poorer quality of life and functional ability. The framework for this dissertation study draws on those hypothesized relationships by examining some of those same factors in association with objective and subjective cognitive dysfunction in older BCS specifically. Cognitive dysfunction is conceptually defined as a complex symptom identified by cognitive changes that negatively affect or alter higher-order mental processes, including but not limited to memory (immediate and delayed), attention, executive functioning-working memory, and verbal fluency [50,51]. In this model and the BCS literature, cognitive dysfunction is operationally defined by both objective and subjective assessments.

Based on the model and the review of literature, the relationship between objective and subjective cognitive function in older BCS was examined (Aim 2a). Demographic (age and education), medical (number of comorbidities), and treatment factors (time post diagnosis and breast cancer stage), and cancer-related symptoms (depressive symptoms, anxiety, fatigue, and sleep disturbance) are included in the model and will be examined in relationship with both objective and subjective cognitive function (Aim 2b) [23,24,34,39]. The model also depicts two potential related sequelae of cognitive dysfunction, physical functioning and QoL (Aim 2c) [23,34,39,41].

Approach

Research Design

Data for this descriptive, secondary data analysis, dissertation study were leveraged from a large, nationwide, American Cancer Society funded-study (RSGPB-04-089-01, PI: Champion) aimed at understanding the unique needs of younger BCS by comparing the QoL of younger BCS to older BCS [52]. Data are from a cross-sectional study in which female BCS who were 3-8 years post-diagnosis completed mailed questionnaires and neuropsychological assessments conducted reliably via telephone [53]. This study reports on the objective and subjective cognitive data that was not reported or published from the original study.

Eligibility Criteria

Inclusion criteria and rationale for this dissertation study included: 1) female gender (breast cancer is rare in men <1% of new diagnoses), 2) 60 years of age and older at diagnosis, 3) 3-8 years from initial diagnosis without a breast cancer recurrence (BCS expressed time of most concern when life should be back to normal; and to avoid confounding factors related to reoccurrence/more homogenous sample), 4) stage I-IIIa at diagnosis (to control for brain metastasis/avoid those with previous use of cranial radiation therapy or intrathecal therapy), 5) able to read and write English (to enable informed consent/participation), 6) received chemotherapy (Adriamycin, Paclitaxel, and Cyclophosphamide) as part of their initial treatment (most at risk for cognitive dysfunction, and 7) had completed the neuropsychological assessment.

Recruitment

Human subjects protection was obtained for the parent study from Indiana University (IU) institutional review board (IRB) and from the local IRB at each of the cooperating sites. Initially, the statistical office for ECOG identified BCS who met eligibility criteria and forwarded the names to the BCS's treating physician. The physician or designee contacted the BCS and asked for permission to forward their name and contact information to researchers at IU. If BCS gave permission for contact, the identifying information for each BCS was sent to researchers. IU then mailed the BCS a brochure explaining the study. One week following this initial mailing, research staff called the BCS to answer any questions and determine interest in participation. If verbal consent was obtained, the BCS was mailed the written informed consent and questionnaire with postage-paid return envelopes. A date was then set for the telephone interview and neuropsychological assessment. Follow-up reminder telephone calls were made if the survey and informed consent were not received within two weeks. If a participant could not be reached by phone and did not return the consent after 10 phone attempts, they were not contacted again.

Sample

In the parent study, younger BCS (age < 45) and older BCS (age 55-70) were approached from Indiana University (IU) and Eastern Cooperative Oncology Group (ECOG) 97 sites, as described in recruitment procedures. Of those BCS approached, a sample of 505 younger BCS and 622 older BCS were recruited and determined to be eligible and consented to the study. This dissertation study only focuses on older BCS; therefore, of the 622 older BCS who were eligible and verbally consented, 491 (79%)

completed and returned study materials including written consent and survey questionnaires. Of those 491 who completed all study materials, 335 (68%) were 60 years of age or older at the time of diagnosis and had completed both the survey questionnaires and objective neuropsychological assessments. Therefore, for this dissertation study, a total of 335 older (≥60 years of age) BCS with complete data were eligible and included in this study.

Data Collection and Management

In the parent study, data was collected primarily by self-report surveys. Trained research assistants then de-identified and entered the data in a password protected database. Neuropsychological assessments were performed by trained staff via the telephone under the direction of a licensed psychologist, expert in neuropsychological assessments, and study coinvestigator. Neuropsychological assessments delivered via the telephone have been found to be reliable and comparable to in-person assessment [53]. Participants received $25 for completing the survey packet and $25 for completing the neuropsychological assessment. To ensure the quality of each neuropsychological assessment the examiner assessed the subject's hearing, comprehension, behavioral and attitudinal responses, telephone connection, extraneous noises, interruptions, and/or abnormal events [53]. The parent study and the resulting data were monitored for quality, recruitment, accrual and retention, outcome and adverse events, and procedures were audited to ensure subject confidentiality. Questionnaires were coded with an identification number so that individuals can only be identified by linking the identification number with the participant list. The participant list for the parent study was secured in a separate password protected database with limited accessibility. For this

dissertation study, all electronic data were de-identified and stored on secure password protected, HIPAA compliant drive accessible only to investigators.

Measures

All assessment measures used in this study are reliable and valid and have been used with BCS. Table 1-1 displays the variables, measures used, number of items, potential score range, reliability of each measure, and scoring interpretation. Most of the neuropsychological assessments have been recommended by the International Cancer and Cognition Task Force and/or are part of the National Institutes of Health toolbox. In the following section, all instruments used in this study will be reviewed [53,54].

Demographic, Medical, and Treatment Factors. Demographic, medical, and treatment data were collected via investigator-initiated questionnaire (self-report) and medical record. Information included age at diagnosis and current age at data collection, race/ethnicity, education, income, marital status, number of comorbidities, specific comorbid conditions, breast cancer diagnosis date and stage, and cancer treatment (surgery, radiation).

Depressive Symptoms. The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item instrument used to assess the presence and severity of depressive symptoms over the past week. Total scores range from 0 to 60, with higher score indicating more depressive symptoms [55,56]. The CES-D has shown satisfactory validity and reliability in the literature and has been widely used in cancer patients including BCS [55-57]. In this study, the Cronbach alpha was .84.

Anxiety. The Spielberger State-Trait Anxiety Inventory (STAI) state subscale is a 20-item instrument assessing state anxiety, or how the participant feels currently on a 4-

point scale ranging from 1 (not at all) to 4 (very much so). Total scores range from 20 to 80, with higher scores indicating more anxiety [58]. This STAI has been established as both valid and reliable and has been widely used in cancer patients including BCS and has been used in previous cognitive studies with BCS [23,39,58]. In this study, the Cronbach alpha was .93.

Fatigue. The Functional Assessment of Cancer Therapy-Fatigue (FACT-F) is a 13-item measure that asks respondents to rate symptoms of fatigue over the last four weeks on a 5-point scale ranging from 0 (not at all) to 4 (very much so) [59]. Total scores range from 0-52 with higher scores indicating more fatigue. The FACT-F was designed and validated for cancer patients, has strong psychometric properties, and has been used extensively with BCS [59]. In this study, the Cronbach alpha was .93.

Sleep Disturbance. The Pittsburgh Sleep Quality Index (PSQI) sleep disturbance subscale is a 9-item measure used to assess sleep disturbances during the past four weeks [60]. Potential scores range from 0 to 3, with higher scores indicating poorer sleep or more sleep disturbance [60]. This measure has been used previously among BCS and had acceptable reliability (Cronbach alpha .70-.80) [38,61,62]. In this study, the Cronbach alpha was .68.

Immediate and Delayed Memory. The Rey Auditory Verbal Learning Test (AVLT) is a word list reading task that is used to test immediate and delayed memory [63]. Participants are presented with a 15-item word list for five learning trials. Immediate recall is taken after each trial. Delayed recall of the initial list is taken 30-minutes later after other assessments have been completed. The immediate memory score is the total number of words recalled all five learning trials, with higher scores indicating

better performance. The delayed memory is the total number of words the individual remembers from the initial list after the 30-minute delay, with higher scores indicating better performance. The AVLT has good test-retest reliability r=.77 (immediate) and r=.60 (delayed) and has been used in BCS [63-66].

Attention and Executive Function-Working Memory. The Wechsler Adult Intelligence Scale IV (WAIS) - Digit Span Forward and Backward is used to assess attention and executive function-working memory, respectively [67]. The subscales of the Digit Span Forward (attention) and Backward (executive function-working memory) will be reported separately as two different cognitive domains in this study. Digit Span-Forward specifically assesses attention. For the Digit Span-Forward test, the tester verbalizes a string of digits and the participant must recite the digit string in the same order it is given. Digit Span-Backward specifically assesses executive function-working memory. For the Digit Span-Backward test, the tester verbalizes a string of digits and the participant must recite the digit string reversing the order. Digit Span uses verbal repetition of digit strings forward and backward that gradually get longer. The score for Forward and Backward separately is the number of digit strings correctly recited with higher scores indicating better functioning. The Digit Span-forward and backward have good test-retest reliability r=.89 and r=.83, respectively [67,68].

Verbal Fluency. The Benton Controlled Oral Word Association Test (COWA) is designed to evaluate the spontaneous production of words beginning with a given letter (e.g. C, F, L) within a limited amount of time. Participants are asked to produce as many words they can think of that begin with the given letter, excluding proper nouns and the same word with a different suffix, in one minute [69]. This instrument is used to assess

verbal fluency, with higher scores indicating better functioning. The COWA has good test-retest reliability r=.70 and has been previously used in BCS [70].

Subjective Attention. Subjective cognitive function (subjective attention) was measured using the Attentional Function Index (AFI), a 13-item self-report instrument used to assess perceived effectiveness in common activities requiring attention, working memory, and executive function on a 0-10 scale, with potential scores ranging from 0-130 [71]. High scores on this instrument indicate better perceived attention function. There are predetermined cut-points used in the literature to indicate level of functioning; <50 indicates low/poor attention function, 50-70 indicated moderate attention function, and >75 indicated good attention function [71]. In this study, the Cronbach alpha was .80.

Physical Function. The Physical Functioning-10 (PF-10) is a subscale of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) [72, 73]. The SF-36, and its subscales including the PF-10, have been established as a comprehensive measure of general health that has shown reliability and validity in various populations, including cancer patients [72]. The PF-10 measures the participants perceived limitations of physical functioning during the past four weeks with a 3-point scale (yes, limited a lot; yes, limited a little; and no, not limited at all), using the original 0-100 scoring with higher scores indicating less limitation or disability [73]. In this study, the PF-10 subscale had a Cronbach alpha of .89.

Quality of Life. The Index of Well-Being–Survivor (IWB) is a 9-item measure used to assess QoL at present time, by asking how the individual feels about their life on a 7-point semantic differential scale, from 1 (boring) to 7 (interesting); 1 (useless) to 7 (worthwhile); or 1 (enjoyable) to 7 (miserable), and so on [74]. Scores range from 2.1 to

14.7, with higher scores indicating better QoL. This instrument was developed to measure specific concerns of long-term cancer survivors, including BCS, and has established reliability and validity [52,73,75]. In this study, the Cronbach alpha was 0.92.

Data Analysis

For this dissertation study, a dataset was created from the database of the parent study. IRB approved data managers retrieved the cases from the original databases that match eligibility criteria. A sample size of 335 BCS who are ≥ 60 years of age and met all eligibility criteria with objective cognitive function data were included. Descriptive statistics appropriate for the measurement level (e.g., frequencies and percentages for nominal/ordinal; mean and standard deviation for interval/ratio) were computed for all variables to ensure data quality, identify out of range values, and evaluate the assumptions of statistical tests including normality and intercorrelation of independent variables and were also be used to describe the sample. Specific data analyses for each aim are presented as follows:

Aim 1: Synthesize the literature regarding cognitive dysfunction in older BCS.

Specifically, examine the prevalence of cognitive dysfunction in older BCS, including both objective and subjective measures and examine factors associated with these measures of cognitive dysfunction.

Analysis for Aim 1: The literature will be reviewed and synthesized using Whittemore and Knafl integrative review methods [76].

Aim 2a: Examine the relationships between objective cognitive function and subjective cognitive function in older BCS.

Analysis for Aim 2a: Pearson correlation (r) will be used to examine the relationships between objective cognitive functioning (immediate and delayed memory, attention, executive function-working memory, and verbal fluency) and subjective cognitive functioning (subjective attention).

Aim 2b: Examine demographic, medical, and treatment factors, and cancer-related symptoms and their relationship with objective cognitive function and subjective cognitive function in older BCS.

Analysis for Aim 2b: Separate multiple linear regressions were computed to examine the relationships between independent variables of demographic (age and education), medical (number of comorbidities), and treatment factors (time since diagnosis and breast cancer stage), and cancer-related symptoms (depressive symptoms, anxiety, fatigue, and sleep disturbance) and dependent variables of objective cognitive function (immediate and delayed memory, attention, executive function-working memory, and verbal fluency) and subjective cognitive function (attention) in older BCS.

Aim 2c: Examine comorbidities, objective cognitive function and subjective cognitive function and their relationship with physical functioning and QoL in older BCS.

Analysis for Aim 2c: Separate multiple linear regressions were computed to examine the relationship between independent variables of age, education, comorbidities, objective cognitive function (immediate and delayed memory, attention, executive function-working memory, and verbal fluency) and subjective cognitive function (attention) and dependent variables of physical functioning and QoL in older BCS.

Sample Size and Power Analysis

The power analysis was based on the statistical approach described above. Table 1-2 below shows power estimates for a performing a linear regression model with continuous variables. Effect size estimates (small, medium and large) were chosen from Cohen (2013) [77]. These effect sizes correspond to estimating a model with an R_2 value of 2% (small), 13% (medium) and 26% (large). Analysis shows the sample of 335 subjects will have sufficient power to detect both medium and large effect sizes for any regression model ranging from one to ten independent variables. The table also shows the smallest effect size (between small and medium) where all possible models will have at least 80% power. This corresponds to an effect size of $f_2 = 0.05$ or R_2 value of 5%.

Conclusion

The overall purpose of this dissertation was to characterize cognitive dysfunction in older BCS. The following chapters will systematically address the aims of the dissertation. Findings from this work will be used to identify older BCS at risk for cognitive dysfunction as well as identify potential interventions to address cognitive dysfunction in older BCS.

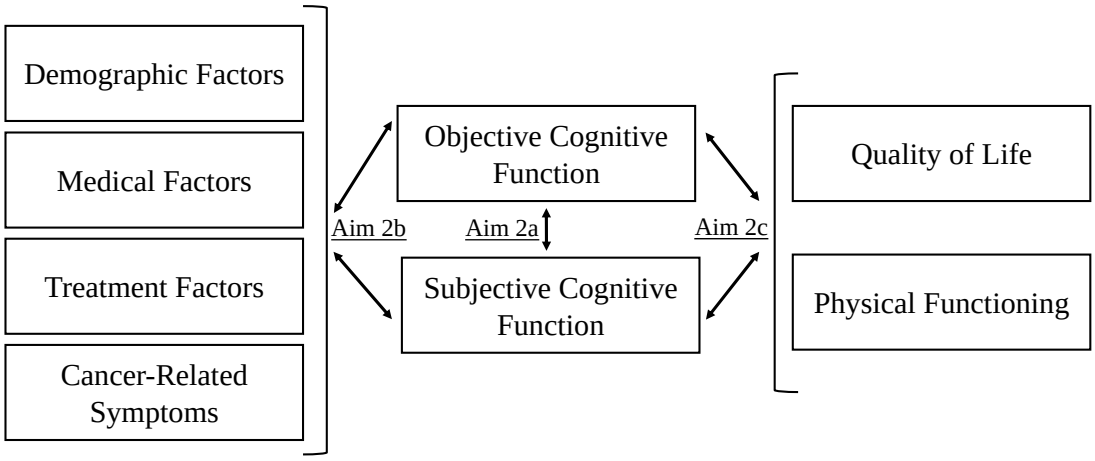

Figure 1-1 Conceptual Framework for Dissertation

Note: This conceptual framework is congruent with the parent study [52] and was derived and modified from Hess and Insel's (2007) Conceptual Model of Cancer-Related Changes in Cognitive Function and from the relevant literature [50].

Table 1-1 Summary of Study Measures

Variable	**Measure**	**No. Items/ (Potential range)**	**Reliability***	**Score**
Demographic	Age	60-70 years old at diagnosis	N/A	N/A
	Education	0-20+ years	N/A	N/A
Medical	Number of comorbidities	0-18+ self-reported comorbid conditions	N/A	N/A
Treatment	Breast cancer stage	I-IIIa	N/A	N/A
	Time post diagnosis	3-8 years	N/A	N/A
Depressive Symptoms	Center for Epidemiologic Studies Depression Scale (CESD) [55]	20 items / (20-60)	α=.84	Higher scores indicate more depressive symptoms. Scores $\geq$ 16 indicate depression
Anxiety	State Trait Anxiety Inventory (STAI) – State subscale [58]	20 items / (20-80)	α=.93	Higher scores indicate more anxiety
Fatigue	Functional Assessment of Cancer Therapy: Fatigue (FACT-F) [59]	13 items / (0-52)	α=.93	Higher scores indicate less fatigue
Sleep Disturbance	Pittsburg Sleep Quality Index (PSQI) – Sleep Disturbance subscale [60]	9 items / (0-3)	α=.68	Higher scores indicate more sleep disturbance-worse sleep
Immediate Memory	Rey Auditory-Verbal Learning Test (AVLT)-Immediate Recall [63]	15 words, 5 trials (0-75)	r=.77	Higher scores indicate better immediate memory
Delayed Memory	Rey Auditory-Verbal Learning Test (AVLT) – Delayed Recall [63]	15 words, 1 trial (0-15)	r=.60	Higher scores indicate better delayed memory
Attention	Wechsler Adult Intelligence Scale IV (WAIS) -	16 number sequences recited forward	r=.89	Higher scores indicate better attention

Variable	Measure	No. Items/ (Potential range)	Reliability*	Score
	Digit Span Forward [67]			
Executive Function-Working Memory	Wechsler Adult Intelligence Scale IV (WAIS) - Digit Span Backward [67]	14 number sequences recited backward	r=.83	Higher scores indicate better executive function-working memory
Verbal Fluency	Controlled Oral Word Association (COWA) [69]	#words/1min	r=.70	Higher scores indicate better verbal fluency
Subjective Attention	Attentional Function Index (AFI) [71]	13 items / (0-130)	α=.80	Higher scores indicate better subjective attention
Physical Functioning	Physical Functioning (PF-10) - Subscale of the Medical Outcomes Study Short Form (SF-36) [72]	10 items / (0-100)	α=.89	Higher scores indicate better physical functioning, less disability
Quality of Life	Index of Well-Being [78]	9 items / (2.1-14.7)	α=.92	Higher scores indicate better QoL

*published test–retest reliability coefficients for neuropsychological assessments and Cronbach alpha from this study for self-report instruments

Table 1-2 Power Estimates for a Multiple Regression Analysis Model

	Number of independent variables				
Effect size	1	2	5	7	10
Small: f_2=0.02, R_2 = 0.02	0.73	0.63	0.47	0.41	0.35
Between small and medium: f_2=0.05, R_2 = 0.05	0.98	0.96	0.90	0.86	0.80
Medium: f_2=0.15, R_2 = 0.13	0.99	0.99	0.99	0.99	0.99
Large: f_2=0.35, R_2 = 0.26	1.00	1.00	1.00	1.00	1.00

Note: (N=335); alpha level set to 0.05; R_2 = percent variance explained by model; f_2 = Cohen effect size for multiple linear regression model.

CHAPTER 2

Introduction

Older breast cancer survivors (BCS) (60 years of age and older) make up approximately 60% of the more than 3.8 million BCS living in the United States, and this number is projected to rise as the nation's population continues to age [17,79,80]. Although some studies suggest that older cancer survivors may be more equipped to deal with the psychological symptoms and burden of a cancer diagnosis and treatment; [80] most studies report that older survivors may have a greater risk for experiencing potentially debilitating side-effects [81-83]. Older BCS may be at an increased risk for developing cognitive dysfunction following cancer diagnosis and treatment due to the normal neurodegenerative effects of aging and the neurotoxic effects of cancer treatment, which has both direct effects as well as has been hypothesized to accelerate the aging process [3,84].

Cognitive dysfunction has been recognized as a prevalent and distressing problem in the BCS of all ages [4,64]. Researchers have documented up to 75% of BCS report cognitive dysfunction, however, less is known regarding cognitive dysfunction in older BCS. Researchers are beginning to recognize that older cancer patients may have unique needs and consequences of cancer related cognitive dysfunction. In fact, a recent position paper by Pergolotti and colleagues (2019) highlighted the needs and consequences older cancer patients may face including comorbidities, polypharmacy, frailty, changes in level of independence, functional and physical abilities, decision making capacity, as well as an increased likelihood of dementia [84,85]. There are many gaps in knowledge

regarding cognitive dysfunction in the older cancer patient population and a critical need for further research to better understand the complexity of the problem [84].

Therefore, the purpose of this integrative literature review was to comprehensively examine cognitive dysfunction in older (60 years of age and older) BCS. Specifically, this review examined the prevalence of cognitive dysfunction in older BCS, including both objective and subjective self-report measures. Additionally, factors associated with these measures of cognitive dysfunction were also examined. Findings from this review elucidated the problem of cognitive dysfunction in older BCS and identify potential modifiable factors that may be associated with cognitive dysfunction in older BCS, which in turn, potentially informing the future development of evidence-based treatment and care for cognitive dysfunction in older BCS specifically.

Methods

An integrative review was conducted to summarize literature regarding the prevalence of cognitive dysfunction and factors associated with cognitive dysfunction in older BCS. The Whittemore and Knafl integrative review method was used as it allows for multiple diverse research designs and methods and includes: 1) problem identification, 2) literature search, 3) data evaluation, 4) data analysis, and 5) presentation of findings [76]. For this review, cognitive dysfunction was defined as a cognitive change that negatively affects high-order mental processes, including executive function, attention, concentration, intelligence, memory, recall, psychomotor ability, processing, verbal ability, vigilance, visuospatial and visuomotor ability [51,50]. Cognitive function may be measured using objective neuropsychological exam and/or subjective self-report measures and both were included in this review.

Eligibility Criteria

Manuscripts included in this review were empirical studies, published in English between 2006 and 2019 in peer-reviewed journals, and included older (60 years of age and older) breast cancer survivors. Older BCS were defined as women with a breast cancer diagnosis who were 60 years of age and older. This definition uses 60 years of age and older, which is congruent with the Centers for Disease Control and federal Older American Act criteria [15]. This review importantly focused on older BCS in this age group, because they make up the majority of new breast cancer cases, are the largest sub-population of BCS, and older BCS are believed to be more susceptible to cognitive dysfunction [16,17]. Studies included in the review were also required to have reliable and valid measure(s) of cognitive dysfunction including objective and/or subjective assessments. Both objective and subjective assessments of cognitive dysfunction are important to the overall understanding of cognitive dysfunction in older BCS. Objective neuropsychological assessments are comprised of performance-based tests to assess various cognitive skills and function and are often considered the gold standard for assessing cognitive dysfunction [54,86]. Subjective assessments, including self-report measures of cognitive dysfunction, are also important to identifying cognitive dysfunction in the clinical setting, are often used as the initial indication for referrals for more in-depth neuropsychological assessments, and have been used in the larger BCS literature to identify subtle indicators of cognitive dysfunction that is not always detected on neuropsychological exam [9,33,87].

Studies were excluded that focused solely on breast cancer survivors with metastatic disease to avoid confounding those with brain metastasis and/or those with

previous use of cranial radiation therapy or intrathecal therapy. In addition, studies with a sole focus on dementia were excluded, as articles examining potentially modifiable associated factors of cognitive dysfunction were of most interest.

Literature Search

Databases used in this review included: PubMed, the Cumulative Index to Nursing and Allied Health Literature - CINAHL, PsycINFO, MEDLINE, and Web of Science. These databases were chosen based upon the subject areas they encompass including nursing, medicine, allied health, and psychology. Data bases were searched for relevant manuscripts from 2004 to 2019 to include literature published over the past 15 years. To capture the older BCS population with cognitive dysfunction, search terms alone and in combination included: “breast cancer,” “breast cancer survivor,” “breast cancer survivorship,” “cognitive impairment,” “cognitive dysfunction,” “older,” “elderly,” “geriatrics,” and “seniors.”

Data Extraction and Analyses

Each article was reviewed by two authors (A.C. and D.V.) to ensure appropriate study inclusion, exclusion, and data extraction. Data from the included studies was extracted, organized, confirmed and displayed in tables. Table 2-1 displays information from each study including: first-author name, publication date, population (n), study design, trajectory (Pre-, During-, and Post-treatment), prevalence of cognitive dysfunction, and factors associated with cognitive dysfunction. Table 2-2 denotes all of the factors examined and which factors were significantly related to either subjective and/or objective cognitive dysfunction in each study in this review.

Results

Search Results

Figure 2-1 depicts the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Search Strategy. A total of 427 articles from four databases were initially identified from the literature search. All references were imported into a reference management program and 80 duplicates were removed, leaving 347 articles remaining for review. Upon reviewing titles for relevance to this review, 194 articles were eliminated because they did not focus on older BCS and/or cognitive functioning. Abstract reviews were completed and 139 more records were removed due to not meeting inclusion criteria: (1) BCS under 60 years of age (n=107), (2) no cognitive measurement (n=12), (3) not English language (n=5), and (4) non-empirical articles (n=15). Fourteen full-text articles were reviewed. After reviewing the reference lists of those articles, another 4 full-text papers were identified. A total of 18 full-text articles were reviewed and 6 studies were eliminated due to: (1) lack of cognitive assessment measure and/or used a dementia diagnosis (n=5) [88-92] and (2) BCS had metastatic disease (n=1) [93].

Articles included in this review were critically examined for their relevance to cognitive dysfunction in older BCS and for their scientific rigor. To date studies have been correlational, observational, and descriptive. Based on the rating system for the hierarchy of evidence for intervention/treatment criteria in Melnyk and Fineout-Overholt (2015), the levels of evidence for the research studies in this review varied ranging from level 4 (correlational, case-control or cohort studies) to level 6 (descriptive or qualitative studies) [94]. There have not been intervention trials, randomized control trials, or systematic reviews conducted in this area to date [94].

Study Characteristics

A total of 12 articles met all eligibility criteria and were included in this review [23,24,34,39,41,43,95-100]. Publication dates ranged from January 2006 to December 2019. Results from the data extraction are summarized in Table 2-1. The 12 studies in this review included 3,384 BCS and 1,197 healthy controls total. Notably, three teams of researchers (Hurria et al., Lange et al., and Mandelblatt et al.) conducted a total of 10 of the 12 studies. Each of the publications included in this review by these three teams of researchers were reviewed and found to present unique objectives and results were not duplicative in nature and thus, add to the body of knowledge in this area and were included in this review. Sample sizes varied significantly, from 28 BCS to 1280 BCS, among the studies reviewed. BCS ranged in age from 60 to 98 years in these studies. All 12 of the studies included in this review are quantitative, observational studies [23,24,34,39,41,43,95-100], with 10 (83%) prospective [23,24,34,41,43,96-100], and two (17%) cross-sectional [39,95]. Of the 10 prospective studies, four studies [34,41,96,99] examined cognitive dysfunction with pre-treatment and post-treatment assessment, 6 studies [23,24,43,97,98,100] were longitudinal examining cognitive dysfunction at multiple time points, including one study which examined cognitive dysfunction annually for up to 7-years post-treatment [23]. Of the two cross-sectional studies, one study [39] examined participants after surgery but before initiation of an adjuvant treatment and one study [95] focused on post-treatment survivorship, including BCS who were ≥10 years post treatment (M=16.8 years post-treatment) with standard chemotherapy.

Measurement of cognitive dysfunction varied across studies. Two of the 12 studies (17%) [41,95] employed only objective cognitive function measures. Three of the

12 studies (25%) [24,96,100] reported only subjective measures of cognitive dysfunction. The majority, seven of the 12 studies (58%) [23,34,39,43,97-99], reported both objective and subjective measures of cognitive function. In total, there were nine studies [23,34,39,41,43,95,97,99,98] that used objective measures of cognitive function and 10 studies [96,34,43,24,39,97-100] that reported subjective measures of cognitive function. In the following section, results for objective cognitive dysfunction, including the prevalence, trajectory and associated factors will be presented, followed by similar results for subjective cognitive dysfunction in older BCS.

Objective Cognitive Dysfunction

Nine studies in this review included objective measures of cognitive function in older BCS [23,34,39,41,43,95,97,98,99]. Although the exact measures varied, most studies included assessments of the following cognitive domains including memory, executive functioning, processing speed, and language/verbal fluency.

Prevalence

Table 2-1 presents the prevalence of objective cognitive dysfunction from each study and the definitions used to designate cognitive dysfunction. In the majority of the literature, significant objective cognitive dysfunction has been defined in the literature and in this review as 1.5 standard deviations (SDs) or 2.0 SDs below norm-based tests or healthy control groups on one or more objective neuropsychological test [101]. Prior to treatment, the prevalence of cognitive dysfunction ranged from 11% to 41% using objective neuropsychological assessments [39,41]. It was reported across studies that cognitive function post-treatment, measured by objective neuropsychological tests, up to 49% in older BCS exhibited cognitive decline [34,41]. Cognitive domains identified as

impaired throughout the studies included memory, executive functioning, and speed of processing.

Patterns emerged when objective cognitive dysfunction was examined over time. Lange and colleagues (2019) [99] identified five patterns of cognitive decline from pre- to post-treatment among 118 older, early stage BCS, 65 years of age and older. All older BCS experienced cognitive decline at differing rates, some declined at a rate similar to normal ageing, while others declined at an accelerated rate with pathological decline, and none improved form pre- to immediately post-treatment.

Associated Factors

Table 2-2 identifies all of the factors that were examined in review of these articles and denotes those which were significantly related to objective cognitive function. Based on the findings, factors associated with objective cognitive dysfunction were grouped into demographic, medical, and treatment factors, cancer-related symptoms, physical/functional factors, and quality of life (QoL), a thorough summary is provided below.

Demographic. Of the nine studies that used objective measures, three [34,39,98] examined the relationship between age and objective cognitive dysfunction with two [34,98] identifying that older age was related to cognitive dysfunction. In Lange et al. (2016) [34], being 70 years of age and older was related to objective cognitive dysfunction, specifically executive functioning. Mandelblatt et al. (2018) [98] found that older age was significantly associated with lower cognitive functioning scores at baseline among 344 older BCS in the study. Only two studies [34,39] that used objective measures

investigated the relationship between education and objective cognitive dysfunction, neither found significant results.

Medical and Treatment. Four studies [34,39,41,98] assessed comorbidities in relationship to objective cognitive dysfunction, one study [98] found significant associations between comorbidity and cognitive dysfunction. Results from the Mandelblatt et al. (2018) study indicate that individuals with more than two comorbid conditions or a diagnosis of diabetes had significantly lower cognitive scores at baseline [98]. Five studies [23,34,39,41,98] assessed type of treatment or therapy in relationship to objective cognitive dysfunction, with two studies [34,98] finding significant relationships. One of those studies by Lange et al. (2016) [34] found that those who received chemotherapy had more objective cognitive dysfunction than those that did not receive chemotherapy but received radiation therapy. Mandelblatt et al. (2018) found similar results in that those who received chemotherapy experienced declines in their cognitive scores over time, specifically in attention, processing speed, and executive function cognitive domains whereas those who did not receive chemotherapy but did receive hormonal therapy improved over time [98].

Two studies [34,39] examined number and type of medications taken. Medications examined were those considered level 3 on the World Health Organization analgesic ladder, anxiolytics, antidepressant treatments, and hypnotics and their association with objective cognitive dysfunction. Results were mixed with one study by Lange and colleagues (2016) [34] found that these level 3 medications were significantly associated with poorer visual episodic memory on neuropsychological exam, while this

relationship was not identified in other cognitive domains nor in an earlier study by this team [39].

Cancer-Related Symptoms. The relationship between objective cognitive dysfunction and anxiety was examined in three of the nine studies [34,39,98], although none found significant associations. Depression or depressive symptoms were assessed in relationship to objective cognitive dysfunction in five studies [34,39,41,95,98], with no significant relationships identified. Fatigue related to objective cognitive dysfunction was examined in three studies [34,39,98], with no significant relationships identified. In one study sleep disturbance was examined in relationship with objective cognitive dysfunction and was significant [97]. Tometich and colleagues (2019) examined objective cognitive dysfunction and the association with cancer-related symptoms (anxiety, depression, fatigue, sleep disturbance, and pain) in 319 older (60 years of age and older) BCS. However, in this study these psychoneurological symptoms were clustered into two groups, high-symptom and low-symptom groups, for analysis [43]. The group with high- psychoneurological, cancer-related symptoms experienced worse objective cognitive dysfunction [43].

Physical/Functional. In three studies [34,39,41] researchers assessed physical function/performance status and two studies [39,98] assessed frailty in relationship with objective cognitive dysfunction. Mandelblatt and colleagues [98] found frailty, measured by an adapted Searle's deficits accumulation index resulting in scores categorized into robust, pre-frail, and frail, to be related to objective cognitive dysfunction; the other study did not find this significant relationship [102]. In three studies [34,39,41] researchers assessed activities of daily living, basic self-care skills that are required to maintain

independent living, and none found significant results related to objective cognitive dysfunction in older BCS.

Quality of Life. QoL, measured by scales specific to cancer diagnosis and treatment, was assessed in two studies [34,41], both studies found significant yet mixed results. Hurria, Rosen, and colleagues [41] found that BCS whose objective cognitive dysfunction worsened from pre-treatment to post-treatment was related to significantly higher QoL scores. The authors hypothesized that although objective cognitive dysfunction worsened from baseline to 6-months after chemotherapy, QoL may have been worse at baseline due to just receiving a cancer diagnosis and likely improved at 6-months after chemotherapy due to finishing treatment [13]. Lange et al. (2016) found an objective decline in at least one cognitive domain was related to the QoL subscale (FACT-Cog) [34].

Subjective Cognitive Dysfunction

Ten of the 12 studies in this review employed a measure of subjective cognitive function [23,24,34,39,43,96-100]. Subjective cognitive functioning was measured in a variety of ways with instruments ranging from two questions from a larger QoL questionnaire (i.e. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QOL-C30)) to a scale focused solely on cognitive functioning in cancer patients with 41 questions and four separate sub-scales (i.e. Functional Assessment of Cancer Therapy - Cognitive Function test (FACT-Cog)).

Prevalence

Table 2-1 presents prevalence of subjective cognitive dysfunction from each study included. Higher prevalence of cognitive dysfunction was noted when subjective

measures were used, with up to 64% reporting cognitive dysfunction prior to adjuvant treatment. Importantly, it was also noted that those older BCS who had poorer cognitive functioning at baseline also had greater cognitive decline after adjuvant treatment, with up to 51% of older BCS reporting a significant decline in their memory post treatment. Freedman et al. (2013) found that subjective cognitive dysfunction increased after treatment, from 6% pre- to 12% post-treatment and at 2-years post-treatment 9% of older BCS reported cognitive dysfunction.

When subjective cognitive dysfunction was examined over time, a few patterns emerged. Mandelblatt and colleagues (2016) [23] identified three patterns of subjective cognitive dysfunction from before to after treatment in 1280 older BCS 65 years of age and older. Older BCS experienced subjective cognitive decline ranging from 'very slight' to 'steep' or 'accelerated' decline from pre- to post-treatment; none improved [23].

Associated Factors

Demographic. Of the nine studies that used subjective cognitive dysfunction measures, five studies [23,24,34,39,98] examined the relationship between age and subjective cognitive dysfunction with one [98] identifying that older chronologic age was associated with lower baseline subjective cognitive function. Only one of the studies [24] which employed subjective measures looked at the relationship of education and subjective cognitive dysfunction and found that lower education level was associated with poorer subjective cognitive dysfunction.

Medical and Treatment. Two studies [23,24] assessed comorbidities in relationship to subjective cognitive dysfunction and both found significant associations between increased number of comorbidities and greater subjective cognitive dysfunction.

Specifically, Mandelblatt and colleagues (2016) found that cardiovascular disease was significantly correlated with accelerated cognitive dysfunction, although this finding did not hold in multivariate analyses [23]. Freedman et al. (2013) found more comorbid conditions to be significantly related to cognitive dysfunction at baseline before treatment [24]. All studies collected information on BCS treatment modalities, five studies [23,24,34,41,98] assessed type of treatment in relationship to subjective cognitive dysfunction and two studies [23,34] found that those who received chemotherapy had more subjective cognitive dysfunction than those that did not receive chemotherapy. Medications and their potential association with subjective cognitive dysfunction were not addressed in any of the studies.

Cancer-Related Symptoms. Three of the nine studies [23,24,39] examined anxiety, all found anxiety to be significantly related to poorer subjective cognitive dysfunction. Three studies [23,24,39] assessed depression or depressive symptoms in relationship to subjective cognitive dysfunction and two of those studies [23,39] found significant relationships with those with more depressive symptoms reporting more cognitive dysfunction. Two studies [24,39] examined fatigue and found that fatigue was significantly related to subjective cognitive dysfunction, where those with more fatigue also reported more cognitive dysfunction. One study [97] assessed sleep disturbance and found a significant relationship between sleep disturbance and subjective cognitive dysfunction. Tometich et al. (2019) examined the association between subjective cognitive dysfunction and a psychoneurological symptom cluster (i.e. anxiety, depression, fatigue, sleep disturbance, and pain), the symptom clusters were separated into two groups high-symptom and low-symptom groups for analysis [43]. The group

with high-psychoneurological, cancer-related symptoms experienced worse subjective cognitive dysfunction [43].

Physical/Functional. One study [23] assessed physical function/performance status and two studies [23,98] assessed frailty in relationship to subjective cognitive dysfunction. Mandelblatt and colleagues (2016) found both worse physical functioning and increased frailty to be related to increased subjective cognitive dysfunction overtime [23]. Mandelblatt et al. (2018) also found frailty to be significantly related to subjective cognitive dysfunction [98]. None of the studies in this review assessed activities of daily living in relationship to subjective cognitive dysfunction.

Quality of Life. QoL was assessed by one study [39], Lange and colleagues (2014) found QOL scores, a FACT-Cog subscale, to be significantly related to subjective cognitive dysfunction on other FACT-Cog subscales, with poorer perceived cognitive dysfunction related to poorer QOL [39]. Mandelblatt et al. (2019) [100] addressed subjective cognitive dysfunction and the impact upon well-being and found that cognitive dysfunction among older BCS did impact physical, functional, and emotional well-being.

Discussion

This integrative review identified and synthesized the current evidence regarding cognitive dysfunction in older BCS including the prevalence and factors associated with objective and subjective cognitive dysfunction. A substantial percentage of BCS were noted to incur objectively measured cognitive dysfunction when compared to healthy, non-cancer controls or published norms. In addition, prevalence rates in these older aged BCS studies were slightly higher than objective cognitive dysfunction prevalence rates published in the all age BCS population [85].

The prevalence of subjective cognitive dysfunction was noted to be higher than objectively measured cognitive dysfunction which is consistent with the larger all age BCS literature [13]. In addition, similar subjective cognitive dysfunction prevalence rates have been noted in all age BCS research [103,104]. Higher prevalence of subjective cognitive dysfunction could be related to the idea that objective neuropsychological assessments may not measure the more subtle cognitive dysfunction incurred by BCS, that subjective assessments of cognitive dysfunction are actually tapping into other factors such as psychological distress, and/or that objective and subjective cognitive dysfunction are independent phenomena in cancer patients [105]. However, both subjective and objective cognitive dysfunction are important and should be considered by health care providers. In fact, recognition and validation of subjective cognitive dysfunction alone has been deemed important for many BCS [87]. National Comprehensive Cancer Network guidelines recommend first using self-report to discern if a patient is experiencing cognitive dysfunction [33]. For older BCS this assessment should take place during the initial geriatric assessment and continue at regular intervals over the cancer care trajectory including survivorship [83,84].

Multiple studies examined cognitive dysfunction pre- to post-treatment or in trajectories with most studies identifying increased prevalence of cognitive dysfunction post-treatment. The majority of older BCS had lower pre-treatment cognitive functioning compared to non-cancer controls and then exhibited varying levels of decline from ‘slight’ to ‘accelerated’ cognitive decline post-treatment. Thus, overall the majority of BCS experience poorer performance in cognitive functioning than their non-cancer control counterparts. These trajectories highlight the need and importance of assessment

and re-assessment to identify any changes in older BCS cognitive functioning over the course of the cancer care trajectory. In addition, older cancer patients have reported healthcare provider's assessment of and maintenance of cognitive ability over the cancer trajectory as highly valued [84].

The studies in this review examined various factors that could potentially be associated with cognitive dysfunction. Empirical studies examined the association of cognitive dysfunction with demographic, medical, and treatment factors, cancer-related symptoms, physical functioning/performance factors, and quality of life. Although results were mixed, objective and subjective cognitive dysfunction was associated with age, comorbidities, chemotherapy receipt, sleep, psychoneurological symptom cluster, frailty, and QoL.

Older age was a significant factor associated with cognitive dysfunction in multiple studies examined, which alone is not novel [34,98]. However, it is important to note that only studies with BCS who were 60 years of age and older were included. This finding suggests the relative significance of age as a factor in cognitive dysfunction in BCS. This is also of particular interest due to the increased life expectancy of the general population, with the fastest growing subpopulation identified as those age 85 years of age and older. This rapidly growing subset of BCS may be at most risk of cognitive dysfunction among older BCS and may need tailored evidence-based interventions aimed at promoting independence and everyday cognitive functioning [106,107].

The overall health of the BCS was also noted to be associated with cognitive dysfunction. This review found that BCS with a higher number of comorbidities had poorer cognitive functioning [23,24,98]. Specifically, some researchers noted that

cardiovascular disease and diabetes in particular were related to cognitive dysfunction. These findings are similar to the larger literature in which cardiovascular disease and diabetes, individually have been linked to cognitive dysfunction [108,109]. Together, this may indicate that those older BCS with either an increased number of comorbidities and/or comorbidities that include cardiovascular disease and diabetes may have an even greater risk for cognitive dysfunction.

Older BCS who take more, or specific types of medications, may also have concerns regarding their cognitive functioning. Although only a couple of studies have examined the link between medication use and objective cognitive dysfunction, researchers noted specifically that medications considered level 3 on the World Health Organization analgesic ladder were related to poorer objective cognitive functioning [34]. This is an important finding to consider as older BCS are at risk for polypharmacy [83]. Assessment and management of medication prescription and adherence as it relates to cognitive dysfunction has largely been ignored in the broader BCS literature and is an important area for further examination in this older BCS sub-population.

Chemotherapy has been studied in the larger all age BCS literature and multiple studies have identified chemotherapy as contributing to cognitive dysfunction, although results have been mixed [110,111]. Chemotherapy has been shown to have direct neurotoxic effects. A review by McDonald and Saykin (2013) of imaging studies in BCS found that those BCS who had undergone chemotherapy treatment consistently showed white and gray matter changes in the brain that were also related to both objective and subjective cognitive dysfunction [112]. As in the larger all age BCS literature, chemotherapy has been examined in relationship to both objective and subjective

cognitive dysfunction in older BCS as well. Researchers have also found chemotherapy receipt to be significantly related to both objective and subjective cognitive dysfunction among older BCS, although results were also mixed. As the population continues to age, more BCS will be exposed to neurotoxic chemotherapy treatments and potentially experience cognitive dysfunction. Assessing the type of treatment, especially chemotherapy, is an important factor to consider due when assessing for cognitive dysfunction in older BCS.

Cancer-related symptoms may also impact cognitive dysfunction. Similar to all age BCS, cancer-related symptoms of anxiety, depression, fatigue and sleep disturbance have been noted to be strongly associated with subjective cognitive dysfunction [103,113]. However, these individual symptoms were not found to be related to objective cognitive dysfunction except for sleep. One study did find that a psychoneurological symptom cluster of anxiety, depression, fatigue, sleep disturbance, and pain was related to both objective and subjective cognitive dysfunction [43]. However, the manuscript does not indicate type of pain or use of pain medication that may have contributed. Overall, though cancer-related symptoms should be assessed in relationship to cognitive dysfunction. There are treatments for some of these other symptoms and resolution of these symptoms may address and alleviate concerns related to cognitive dysfunction.

Sleep disturbance was one of the main symptoms noted in findings for both objective and subjective cognitive dysfunction in older BCS. Similar results have been noted in all age BCS with sleep disturbance negatively associated with cognitive dysfunction [35,37,38,114]. This finding is important as older adults are already at a greater risk for sleep disturbances making this an important area for assessment and

surveillance in cancer care with the implications on cognitive functioning [115,116]. Studies of older adults report that short or long sleep duration and/or having sleep complaints or disturbances such as difficulty falling or staying asleep have an increased risk of cognitive dysfunction [117]. In addition, sleep disturbance may be amenable to treatment, if sleep is improved, cognitive dysfunction in this older BCS population could be minimized.

Although results were mixed, decreased physical functioning and increased frailty were significantly related to cognitive dysfunction. These relationships may have significant implications for older BCS. Research in the general aging population has identified that physical limitations, frailty, and cognitive dysfunction combined can have serious ramification for older adult's ability to live independently making these relationships increasingly important in older BCS [107,118]. In addition, these negative implications to independence can require significant time and economic cost to families as well as society [118].

QoL or well-being was significantly related to both subjective and objective cognitive dysfunction. This finding highlights the importance of addressing cognitive dysfunction and its ramifications in older BCS which, has been understudied. QoL is an important area of focus for older adult cancer patients as researchers have shown that decreased QoL in older cancer patients impacts function, disability, treatment continuation, and survival [119]. These consequences underscore the importance of the relationship between cognitive dysfunction and QoL in the older BCS.

Strengths and Limitations

In this review, the literature regarding cognitive dysfunction in older BCS was synthesized, who make up the majority of the total BCS population. This review identifies factors that are associated with cognitive dysfunction and lays the groundwork for evidence-based interventions for older BCS that both focus on reducing factors that impede brain capacity and promote cognitive reserve [120]. There are limitations of this review that are also worth noting. Multiple studies had small samples and two studies had samples under 30 BCS. Although, each study included in this review reported different outcomes or timeframes, it was clear that three main research teams conducted the trials and therefore, may have utilized the same samples (e.g. published baseline in one manuscript and trajectory overtime in another manuscript). This may have limited the scope and generalizability of the findings, yet each contributed independently to what is known regarding cognitive dysfunction in older BCS. In addition, research teams varied in their use of cognitive measures making it difficult to compare cognitive dysfunction in older BCS across multiple studies.

Implications for Future Research

This review identified important research needs. More reach is needed that examines cognitive dysfunction among older BCS across the cancer care trajectory. Most of the studies were limited and failed to examine cognitive dysfunction beyond a few years post-treatment in older BCS. Future research needs to address the long-term concerns of cognitive dysfunction of older BCS. In addition, evaluation of cognitive dysfunction varied between studies making comparisons difficult. Researchers need to use the international recommendations identified by the International Cancer and

Cognitive Task Force [54]. This review also identified some correlated symptoms that are common in all age BCS as well as some unique factors associated with cognitive dysfunction in older BCS. Older BCS may have a higher number of comorbidities, especially diabetes and cardiovascular issues, which may confound the issues associated with cognitive dysfunction. Issues of polypharmacy, sleep disturbance, and psychoneurological symptom clusters should be examined for contributing to cognitive dysfunction in older BCS. In addition, ramifications of cognitive dysfunction including physical limitations, frailty, and decrements in quality of life may be important endpoints for future research. Interventions are needed to mitigate, prevent, and/or slow cognitive dysfunction in older BCS. Interventional research for cognitive dysfunction should be tailored to the specific needs of older individuals and may need to target multiple factors to support cognitive capacity.

Implications for Oncology Nursing Practice

For oncology nursing practice, the findings of this review help to highlight the prevalence of cognitive dysfunction in older BCS as well as describing some factors that could be related to cognitive dysfunction that are important to consider in clinical practice. Assessment, surveillance, and management of comorbid conditions in older BCS is of particular importance for nursing. A thorough geriatric assessment should be a key component of the cancer care continuum for older BCS [83,84,120]. Cognitive dysfunction before, during, and after breast cancer diagnosis and treatment should be a target for assessment and treatment for healthcare providers, especially in older BCS.

Conclusion

To my knowledge, this is the first integrative review to examine the prevalence of cognitive dysfunction and factors associated with cognitive dysfunction in the older BCS population. By collecting and synthesizing the current evidence and presenting the gaps in knowledge, this review is relevant to both clinical practice and research. Findings from this review indicate both objective and subjective cognitive dysfunction are a significant concern that warrants attention in older BCS, although the literature to date is limited. Cognitive dysfunction can be associated with numerous factors as evidenced by the findings of this review. Of particular interest in the older BCS population specifically, would be older age, increased number of comorbidities, as well as specific comorbidities such as diabetes and cardiovascular issues, chemotherapy receipt, sleep, psychoneurological symptom cluster, frailty, and QoL as older adults tend to experience more of these issues than younger adults [107]. Many factors related to cognitive dysfunction identified by this review may be magnified in the older BCS and should be incorporated in a thorough comprehensive geriatric assessment at each cancer appointment [83].

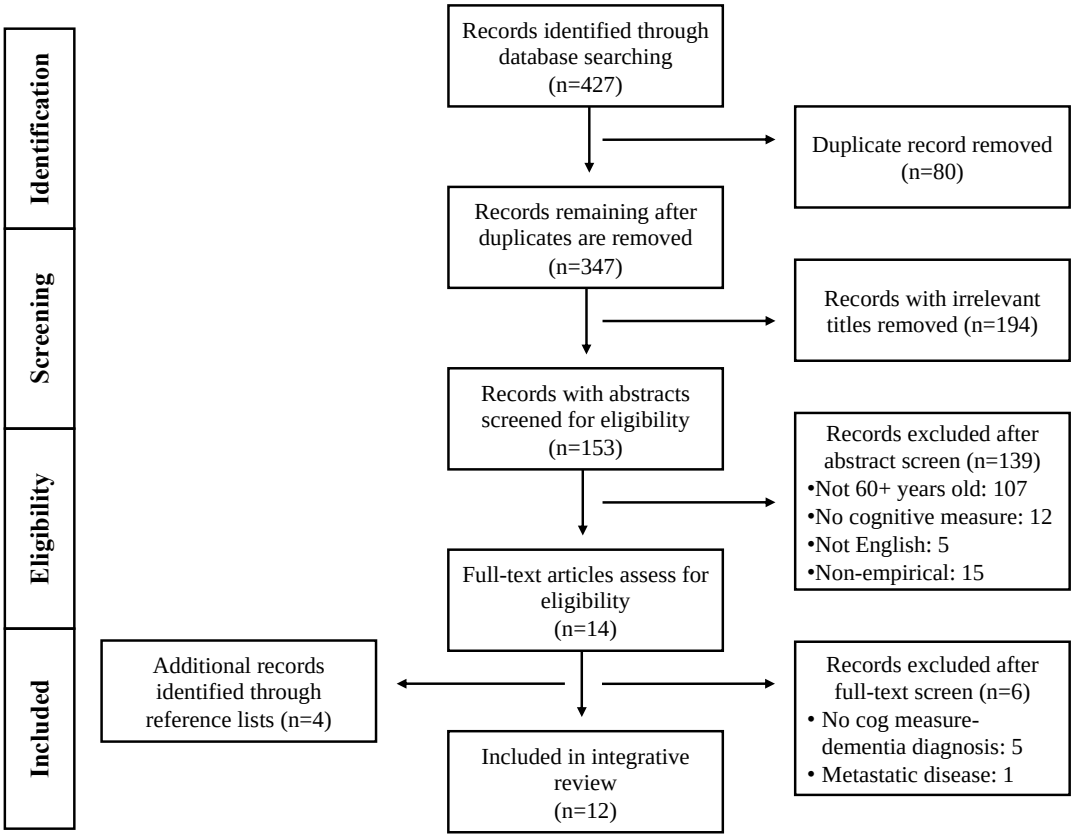

Figure 2-1 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Search Strategy

Table 2-1 Articles Examining Cognitive Dysfunction in Older Breast Cancer Survivors

First Author (Year Published)	Population (n)	Study Design	Trajectory (Pre, During, Post)	Prevalence	Associated Factors
Hurria, Goldfarb (2006)	Stage I-III, receiving adjuvant CT, aged 65+ (n=45 BCS)	Prospective, pre-post, observational	Pre – Post Assessments took place before and 6 months post CT	**Objective:** No objective cognitive measure used **Subjective:** • 64% reported poor memory prior to CT • 51% reported a decline in memory at 6 months post CT • Learning new information was most affected	**Objective:** N/A **Subjective:** No significant associated factors were identified
Hurria, Rosen (2006)	Stage I-III, receiving adjuvant CT, aged 65+ (n=28 BCS)	Prospective, pre-post, observational	Pre – Post Assessments took place before and 6 months post CT	**Objective:** • 11% scored 2 SDs below the norm on 2 or more tests prior to CT at baseline • 29% scored 2 SDs below the norm on 2 or more tests at 6 moths post CT • Domains most affected were visual memory, spatial function, psychomotor function, and attention • *BCS were classified as having CD if they scored ≥ 2 SDs below published norms on ≥ 2 tests* **Subjective:** No subjective cognitive measure used	**Objective:** • QoL **Subjective:** N/A
Yamada (2010)	Stage I-IIIA, aged 65+ (n=30BCS)	Cross-sectional, observational	Post Assessment took place 10+	**Objective:** No objective prevalence was reported • BCS scored significantly lower in executive functioning, working memory,	**Objective:** No associate factors were reported

First Author (Year Published)	Population (n)	Study Design	Trajectory (Pre, During, Post)	Prevalence	Associated Factors
	(n=30 NCC)		years (M=16.8 years) post-treatment	psychomotor speed, and divided attention compared to NCC **Subjective:** No subjective cognitive measure used	**Subjective:** N/A
Freedman (2013)	Stage I-III, receiving standard CT or capecitabin, aged 65+ (n=297 BCS)	Prospective, longitudinal, observational	Pre - During - Post Assessments took place pre-treatment, mid-treatment, end of treatment, 12 months post, 18 months post, and 24 months post treatment	**Objective:** No objective cognitive measure used **Subjective:** • 6% reported CD prior to treatment at baseline • 6% reported CD mid-treatment • 10% reported CD at the end of treatment • 12% reported CD at 12 months post treatment • 7% reported CD 18 months post treatment • 9% reported CD at 24 months post treatment	**Objective:** N/A **Subjective:** (at baseline) • Education • Positive nodes • Comorbidities • Anxiety • Fatigue
Lange (2014)	Newly diagnosed, early-stage, aged 65+ (n=123 BCS)	Cross-sectional, observational	Pre Assessment took place before adjuvant treatment after surgery	**Objective:** • 41% had CD prior to treatment • 29% exhibited CD on 1 test • 12% exhibited CD on 2 or more tests • *CD was defined as a z-score of ≤ 1.5 SDs on 2 or more tests, or a z-score of ≤ 2.0 SDs on 1 test* **Subjective:**	**Objective:** • Subjective CD (*only with verbal episodic memory*) **Subjective:** • Verbal episodic memory dysfunction • Depression • Anxiety • Fatigue

First Author (Year Published)	Population (n)	Study Design	Trajectory (Pre, During, Post)	Prevalence	Associated Factors
				• NCC had more complaints on Perceived CD and Cognitive Abilities FACT-Cog subscales than BCS • BCS had more complaints than NCC on the subscale Impact on Quality of Life of CD	• QoL
Lange (2016)	Newly diagnosed, early-stage, aged 65+ (n=119 BCS; 58 CT+, 61 CT-) (n=62 NCC)	Prospective, pre-post, observational	Pre – Post Assessments took place after surgery but before the start of adjuvant therapy(T1) and after the end of the first adjuvant CT or radiotherapy (T2)	**Objective:** • 41% had CD prior to treatment at baseline • 49% experienced cognitive decline between T1 and T2 in at least 1 domain • *CD was defined as 1.645 SDs below NCC in at least 1 domain based upon reliable change index* **Subjective:** • BCS with more subjective CD at T1 were those who reported greater subjective CD at T2 (not clinically significant)	**Objective:** • Subjective cognitive complaints • Age (executive function) • CT treatment (executive function) • Medications (visual episodic memory) • QoL (decline in at least 1 domain) **Subjective:** • Subjective cognitive complaints were predictive of objective cognitive decline • CT treatment
Mandelblatt (2016)	Newly diagnosed, nonmetastatic, invasive BC (n=1280 BCS)	Prospective, longitudinal, observational	Pre – Post Assessments occurred within 20 weeks of surgery with	**Objective:** • Cognitive screen using Blessed Orientation-Memory-Concentration (BOMC) test **Subjective:**	**Objective:** • Subjective CD (cognitive screen) **Subjective:** • Multiple comorbidities

First Author (Year Published)	Population (n)	Study Design	Trajectory (Pre, During, Post)	Prevalence	Associated Factors
			follow-up at 6 months, 12 months and then annually for up to 7 years	3 trajectory groups noted • 42% were in the 'maintained high' group (good cognitive function baseline – decline = normal aging) • 50% were in the 'phase shift' group (lower cognitive function at baseline – decline = normal aging) • 8% were in the 'accelerated decline' (lower cognitive functioning baseline – steep decline > normal aging)	• CT • Depression • Anxiety • Frailty • Physical function
Mandelblatt (2018)	Newly diagnosed, nonmetastatic, aged 60+, w/o dementia or neurologic disease (n = 344 BCS) (n = 347 NCC)	Prospective, longitudinal, observational	Pre – Post Assessments occurred during pre-systemic treatment, 12 months, and 24 months	**Objective:** No objective prevalence was reported **Subjective:** No subjective prevalence was reported	**Objective:** • Subjective CD • Age • Treatment • Comorbidity • Frailty **Subjective:** • Objective CD • Age • Frailty
Carroll (2019)	Newly diagnosed, nonmetastatic BC, aged 60+ (n=319 BCS)	Prospective, longitudinal, observational	Pre – Post Assessments occurred during pre-systemic treatment, 12	**Objective:** No objective prevalence was reported **Subjective:** No subjective prevalence was reported	**Objective:** • Sleep disturbance • APOE ε4 carrier status **Subjective:** • Sleep disturbance • COMT gene

First Author (Year Published)	Population (n)	Study Design	Trajectory (Pre, During, Post)	Prevalence	Associated Factors
			months, and 24 months		
Lange (2019)	Newly diagnosed, early-stage, aged 65+, (n=118 BCS) (n=62 NCC)	Prospective, pre-post, observational Post hoc analysis of Lange (2016)	Pre – Post Assessments took place after surgery but before the start of adjuvant therapy (T1) and after the end of the first adjuvant CT or radiotherapy (T2)	**Objective:** 5 trajectory groups noted • 15% had 'normal aging' (cognitive function = NCC at baseline – decline = normal aging/NCC) • 12% had 'nonpathological decline' (cognitive function = NCC at baseline – decline slightly > NCC/normal aging but not to the level of CD) • 31% had 'pathological decline' (cognitive function = NCC at baseline – decline > NCC/normal aging resulting in CD) • 36% had 'phase shift hypothesis' (CD at baseline – decline = NCC/normal aging) • 6% had 'accelerated aging hypothesis' (lower cognitive functioning baseline – steep decline > NCC/normal aging) **Subjective:** No subjective prevalence was reported	**Objective:** No associated factors were reported **Subjective:** No associated factors were reported
Mandelblatt (2019)	Newly diagnosed, nonmetastatic BC, aged 60+ (n=362 BCS)	Prospective, longitudinal, observational	Pre – Post Assessments occurred during pre-systemic	**Objective:** No objective cognitive measure reported **Subjective:**	**Objective:** N/A **Subjective:**

First Author (Year Published)	Population (n)	Study Design	Trajectory (Pre, During, Post)	Prevalence	Associated Factors
	(n = 349 NCC)		treatment, 12 months, 24 months, and 36 months post-treatment	Older BCS reported significantly more cognitive problems than NCC	Self-reported cognitive problems had a significant impact on well-being (physical, functional, emotional)
Tometich (2019)	Newly diagnosed, nonmetastatic BC, aged 60+ (n=319 BCS) (n=347 NCC)	Prospective, longitudinal, observational	Pre – Post Assessments occurred during pre-systemic treatment, 12 months, and 24 months	**Objective:** No objective prevalence was reported **Subjective:** No subjective prevalence was reported	**Objective:** • High psychoneurological symptoms (anxiety, depression, fatigue, sleep disturbance, pain) **Subjective:** • High psychoneurological symptoms (anxiety, depression, fatigue, sleep disturbance, pain)

BCS = breast cancer survivor; BC = breast cancer; CD= cognitive dysfunction; CT = chemotherapy; QoL = quality of life; ADL = activities of daily living; NCC = non-cancer control

Table 2-2 Factors Associated with Subjective or Objective Cognitive Dysfunction in Older Breast Cancer Survivors

Study ↓	Demographic		Medical and Treatment			Cancer-Related Symptoms					Physical/Functional			QoL
	Age	Education	Comorbidities	Treatment	Medication	Anxiety	Depression	Fatigue	Sleep	Psychoneurological Cluster	Physical Function	Frailty	ADLs	QoL Well-being
Objective Cognitive Measures														
Hurria, Rosen (2006)			X	X			X				X		X	**X+**
Yamada (2010)							X							
Lange (2014)	X	X	X	X	X	X	X	X			X	X	X	
Lange (2016)	**X+**	X	X	**X+**	**X+**	X	X	X			X		X	**X+**
Mandelblatt (2016)				X										
Lange (2019)														
Mandelblatt (2018)	**X+**		**X+**	**X+**		X	X	X				**X+**		
Carroll (2019)									**X+**					
Tometich (2019)										**X+**				
Subjective Cognitive Measures														
Hurria, Goldfarb (2006)				X										

Study ↓	Demographic		Medical and Treatment			Cancer-Related Symptoms					Physical/Functional			QoL
	Age	Education	Comorbidities	Treatment	Medication	Anxiety	Depression	Fatigue	Sleep	Psychoneurological Cluster	Physical Function	Frailty	ADLs	QoL Well-being
Freedman* (2013)	X	**X+**	**X+**	X		**X+**	X	**X+**						
Lange (2014)	X					**X+**	**X+**	**X+**						**X+**
Lange (2016)	X			**X+**										
Mandelblatt (2016)	X		**X+**	**X+**		**X+**	**X+**				**X+**	**X+**		
Lange (2019)														
Mandelblatt (2018)	**X+**			X								**X+**		
Carroll (2019)									**X+**					
Mandelblatt (2019)														**X+**
Tometich (2019)										**X+**				

X = was examined, non-significant; **X+** = significant in that study; * = measured at baseline only; QoL = quality of life

CHAPTER 3

Introduction

Up until recently older individuals were excluded from many cancer studies and are still underrepresented in cancer research as a whole [121]. With the rapidly growing number of older adults, there is an increased need for research in this population [16]. In addition, with improved prevention, screening, and treatment for cancer, more older adults are receiving treatment and older survivors are living longer after treatment [17,106]. Older BCS face many unique care needs during their diagnosis and treatment for breast cancer, some of which may linger into survivorship and may be compounded with normal aging [122]. One issue older BCS may face is cognitive dysfunction [98,122].

Cognitive dysfunction is a common concern among all age BCS. Older BCS may be at an increased risk due to a number of factors, including normal aging processes, lower cognitive reserve, and the neurotoxic effects of cancer treatment [3]. Cognitive dysfunction has been defined as a complex symptom identified by cognitive changes that negatively impact higher-order mental processes including immediate memory, delayed memory, attention, executive function-working memory, and verbal fluency, which are commonly impaired cognitive domains in all aged BCS. Cognitive dysfunction is measured in BCS by both standardized objective (neuropsychological) assessments and subjective (self-report) assessments. The association between objective and subjective cognitive dysfunction measures has been examined in all age BCS with most studies indicating that they are unrelated [113,123]. However, this relationship has not been fully examined in older BCS. Both objective and subjective measures are important and have

their uses. Self-report is often used in the clinical setting and is often the first indication from the BCS that there is a significant problem for the healthcare provider to address [33,42]. Depending upon the severity of the problem or level of concern, a neuropsychological assessment may be warranted [42]. Thus, understanding the relationship between objective and subjective cognitive assessments may assist in fully characterizing cognitive dysfunction in the older BCS.

Examining factors that may be associated with both objective and subjective cognitive dysfunction is crucial. This information may be critical to identifying factors that are common, overlapping, or compounding. Ultimately, this information may signal a potential risk for cognitive dysfunction and/or may lead to identifying factors that would be amenable to intervention in the older BCS. Identifying factors related to cognitive dysfunction will also be useful for intervention development in older BCS specifically.

Based upon a modified Hess and Insel conceptual framework (which identifies potential antecedents associated with cognitive dysfunction in cancer survivors) [50] and the larger BCS literature, there are factors that may be significantly related to cognitive dysfunction and help to identify and characterize cognitive dysfunction in older BSC [50]. Demographic (age and education), medical (comorbidities), and treatment factors (time since diagnosis and breast cancer stage), have been shown to be significantly related to cognitive dysfunction [23,24,34,98]. In addition, other cancer-related symptoms, including depressive symptoms, anxiety, fatigue, and sleep disturbance have been previously linked with cognitive dysfunction [23,24,39,97]. However, in the all age BCS and the smaller volume of literature focusing on older BCS, these findings have

been mixed. In addition, studies in the older BCS have only followed BCS for up to 2-3 years post-diagnosis, and; thus, have failed to elucidate significant factors associated with cognitive dysfunction in older BCS who further into survivorship and may be experiencing longer term symptoms or late effects of treatment [122].

With the gaps in knowledge, mixed results, and the limited research in the older (60 years of age and older) BCS population and even further limited research in the time span of 3-8 years post diagnosis in older BCS, more research is needed to better understand this complex symptom in older BCS. Therefore, the purpose of this study is to examine the relationships between objective and subjective cognitive dysfunction and factors potentially associated with both subjective and objective cognitive dysfunction in older BCS. Specific aims are to examine the relationships between: 2a) objective cognitive function and subjective cognitive function in older BCS, and 2b) demographic (age and education), medical (comorbidities), and treatment factors (time since diagnosis and breast cancer stage), and cancer-related symptoms (depressive symptoms, anxiety, fatigue, and sleep disturbance) and objective cognitive function (immediate memory, delayed memory, attention, executive function-working memory, and verbal fluency) and subjective cognitive function (subjective attention) in older BCS.

Methods

A descriptive, secondary data analysis study design was used. Cross-sectional data for this dissertation study were leveraged from a large, United States wide BCS study titled “Quality of Life in younger Breast Cancer Survivors” (American Cancer Society RSGPB-04-089-01, PI: V. Champion). The overall aim of the original study was to better understand quality of life in younger versus older BCS [52].

Population and Data Collection

Participants were eligible for this dissertation study if they were: 1) female BCS, 2) 60 years of age and older at the time of breast cancer diagnosis, 3) 3-8 years post-diagnosis at the time of survey completion/data collection without a recurrence or other cancers (exception skin cancer), 4) stage I-IIIa at initial breast cancer diagnosis, 5) able to read and write English, 6) treated with a chemotherapy as part of their initial treatment regimen (Adriamycin, Paclitaxel, and Cyclophosphamide), and 7) completed the neuropsychological assessment.

Participants were recruited from Indiana University (IU) and 97 Eastern Cooperative Oncology Group (ECOG) sites across the United States. Human subjects protection was obtained for the study from IRBs at each cooperating site. Potential participants were identified by the statistical center of the ECOG who in turn notified the BCS's treating physician, who obtained permission to forward their name and contact information to study staff. BCS were mailed information explaining the study and then were contacted via telephone. Interested BCS were then mailed an informed consent and questionnaire with postage-paid return envelopes and a date was set for the telephone neuropsychological assessment. Trained research assistants then de-identified and entered the data in a password protected database. Neuropsychological assessments were performed by trained staff via the telephone under the direction of a licensed psychologist, expert in neuropsychological assessments, and study coinvestigator. Participants received $25 for completing and sending back the survey and $25 for completing the telephone neuropsychological assessment.

Measures

Demographic, Medical, and Treatment Factors. Demographic, medical, and treatment data were collected via investigator-initiated questionnaire (self-report) and medical record. This information includes age at initial breast cancer diagnosis and current age at data collection, race/ethnicity, education, income, marital status, number of comorbidities, self-reported specific comorbid conditions, breast cancer diagnosis date and stage, and cancer treatment (surgery, radiation).

Cancer-Related Symptoms. Cancer-related symptoms included instruments measuring depressive symptoms, anxiety, fatigue, and sleep disturbance. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a 20-item instrument, that assesses the presence and severity of depressive symptoms over the past week, potential scores range from 0-60, with higher scores indicating more depressive symptoms [55,56]. In this study, the CES-D had a Cronbach alpha of .84. Anxiety was measured using the Spielberger State-Trait Anxiety Inventory (STAI)-State sub-scale, a 20-item scale assessing state anxiety at this moment, potential scores range from 20-80, with higher scores indicating more anxiety [58]. In this study, the STAI-State sub-scale had a Cronbach alpha of .93. Fatigue was measured using the Functional Assessment of Cancer Therapy-Fatigue (FACT-F), a 13-item measure, that assesses symptoms of fatigue over the last four weeks, potential scores range from 0-52, with higher scores indicating less fatigue [59]. In this study, the FACT-F had a Cronbach alpha of .93. Sleep was measured using the Pittsburgh Sleep Quality Index (PSQI) - sleep disturbance sub-scale, a 9-item sub-scale, used to assess sleep disturbances during the past four weeks, with potential scores ranging from 0-3, with

higher scores indicating more sleep disturbance or worse sleep [60]. In this study, the PSQI-sleep disturbance subscale had a Cronbach alpha of .65.

Objective Cognitive Function. Objective cognitive function, including immediate memory, delayed memory, attention, executive function-working memory, and verbal fluency were measured using a neuropsychological battery. All of the neuropsychological assessments used in this study are reliable, valid, have been used in BCS, and were performed via telephone by trained staff. Immediate and delayed memory was assessed using the Rey Auditory-Verbal Learning Test (AVLT). The AVLT is a 15-item, five trial word list learning task [63,65,66]. For the AVLT, the tester says the 15 words in the list and the participant tries to remember the words. Immediate memory is the sum of the five learning trials and delayed memory is a free recall of the list approximately 30 minutes later, higher scores on both indicate better functioning. Attention and executive function-working memory were assessed using the Wechsler Adult Intelligence Scale IV (WAIS) - Digit Span Forward and Backward (respectively), a reliable assessment used previously in BCS [67,68]. The subscales of the Digit Span Forward (attention) and Backward (executive function-working memory) will be reported separately as two difference cognitive domains in this study. Digit Span-Forward specifically assesses attention. For the Digit Span-Forward test, the tester says a string of digits and the participant must recite the digit string in the same order it is given. Digit Span-Backward specifically assesses executive function-working memory. For the Digit Span-Backward test, the tester says a string of digits and the participant must recite the digit string in the reverse order it is given. Digit Span uses verbal repetition of digit strings forward and backward that gradually get longer. The score for Forward and

Backward separately is the number of digit strings correctly recited, higher scores indicate better functioning. Verbal fluency was measured using the Controlled Oral Word Association Test (COWA), a reliable measure consistently used in the BCS population [69,70,124]. For the COWA test, the tester gives a letter of the alphabet and the participants tries to produce as many words they can think of that begin with the given letter in 1-minute, higher scores indicate better functioning.

Subjective Cognitive Function. Subjective cognitive function was measured using the Attentional Function Index (AFI). The AFI is a 13-item scale used to assess perceived effectiveness in common activities requiring attention, working memory, and executive function at the present time [71]. Potential scores on the AFI range from 0-130, with higher scores indicating better attention or subjective cognitive functioning [71]. In this study, the AFI had a Cronbach alpha of .80. There are predetermined cut points for the AFI used in the literature to indicate level of attention functioning; <50 indicates low/poor attention function, 50-70 indicated moderate attention function, and >75 indicated good attention function [71].

Statistical Analysis

Descriptive statistics were computed for sociodemographic, medical, and treatment variables to describe the sample. Descriptive statistics were also computed to ensure data quality, identify out of range values, and evaluate the assumptions of statistical tests including normality and intercorrelation of independent variables. Level of significance was set at 0.05. SPSS statistical software, version 26 was used for all data analysis.

Prevalence of cognitive dysfunction on each neuropsychological assessment was determined by creating then comparing z-scores for each assessment for older BCS and a comparison group of non-cancer controls (NCC). Data for the NCC was provided by the Indiana Alzheimer Disease Center Clinical Core Study, a database that includes data from healthy older adult participants with no known neurological disease. NCC data from the Indiana Alzheimer Disease Center was used for comparison because the studies used the same neuropsychological battery, presented in the same order and format, thus, exposing participants to a comparable level of fatigue when testing. In addition, NCC subjects were sex- (female) and age-match (within +/- 5 years) to the BCS sample, providing a better comparison group than published normative data [125]. Based on the literature, 3 cut-point scores of cognitive dysfunction were derived including 1.0 SD (<16th percentile) below the mean or 'mild dysfunction', 1.5 SD (< 7th percentile) below the mean or 'mild-moderate dysfunction', and 2.0 SDs (<2nd percentile) below the mean or 'moderate dysfunction [126]. We created groups for BCS at each cut point to document prevalence of cognitive dysfunction [126]. In clinical practice, it is commonly accepted to use the 16th percentile or 1.0 SD below the mean, as cutoff score for 'abnormality' [126]. Count and percent of BCS within each group were calculated for each test. The AFI has cut points for attention functioning published. We used these cut points in order to provide count and percent of BCS within each level of function, from low/poor attention function to good attention function [71].

The accomplish aim 2a, Pearson bivariate correlations were used to examine the relationship between objective and subjective cognitive functioning**.** To accomplish aim 2b, separate multiple linear regression models were used to examine the relationship

between the independent variables (demographic factors [age at neuropsychological assessment and number of years of education], medical factors [number of comorbidities], treatment factors [time since diagnosis and breast cancer stage], and cancer-related symptoms [depressive symptoms, anxiety, fatigue, and sleep disturbance]) and dependent variables of objective cognitive function (immediate and delayed memory, attention, executive function-working memory, and verbal fluency) and subjective cognitive function (attention) in older BCS.

Results

Participants included 335 older BCS in this study who ranged from 60 to 70 years of age and were on average 63.85 (SD 2.97) years old at the time of their breast cancer diagnosis and were on average 69.79 (SD 3.34) years old at the time of data collection. Table 3-1 reflects the demographic, medical and treatment characteristics of the older BCS in this sample in full detail. At the time of survey and neuropsychological assessment completion older BCS were on average 5.95 (SD 1.48) years post-diagnosis. At initial diagnosis, most of the older BCS had stage II breast cancer (n=227; 67.7%). The majority of the BCS included in this study were White (n=313; 93.4%), married (n=218; 65.1%), educated with at least some college (n=173; 51.6%), and had an income of less than $50,001 per year (n=194; 57.9%). All older BCS received chemotherapy as part of their initial treatment; the majority had a mastectomy (n=178; 53.1%) and radiation therapy (n=203; 60.6%) as part of their breast cancer treatment regimen. In addition, age, education, and race information from the NCCs, used for calculating dysfunction prevalence for each neuropsychological assessment, is included in Table 3-1.

NCCs (n=228) were on average 64.21 (SD 6.08) years of age, had on average 15.34 (SD 2.84) years of education, and were mostly White (n=180; 80.3%).

Table 3-2 presents descriptive information including mean, standard deviation (SD), potential and actual score range for the cancer-related symptoms (depressive symptoms, anxiety, fatigue, and sleep disturbance). For depressive symptoms, scores at or above 16 indicate depression. Overall, the mean for depressive symptoms in this sample is 8.73 (SD 7.83); however, 16.8% (n=56) of the older BCS did have depressive symptom scores at 16 or over indicating depression. For the other symptoms, anxiety, fatigue, and sleep disturbance, there are not validated cut scores to report, but descriptive information can be found in Table 3-2.

Older BCS demonstrated cognitive dysfunction with levels ranging from mild (1 SD), mild to moderate (1.5 SD), and moderate (2 SDs) below NCC for each neuropsychological assessment [126]. Table 3-3 depicts mean, standard deviation (SD), potential and actual score range, and the percentage of older BCS and NCCs within each level of cognitive dysfunction. Only dysfunction for older BCS will be described below. For immediate memory (AVLT), older BCS demonstrated significant dysfunction with 27.8% (n=93) ‘mild’, 12.9% (n=43) ‘mild-moderate’, and 5.7% (n=19) ‘moderate’ dysfunction. For delayed memory (AVLT), older BCS demonstrated significant dysfunction with 19.2% (n=64) ‘mild’, 11.1% (n=37) ‘mild-moderate’, and 3.3% (n=11) ‘moderate’ dysfunction. For attention (Digit Span-Forward), older BCS demonstrated significant dysfunction with 4.2% (n=14) ‘mild’ dysfunction, no older BCS in this sample scored 1.5 SD or 2 SDs below NCC. For executive function-working memory (Digit Span-Backward), older BCS demonstrated significant dysfunction with 9.9%

(n=33) ‘mild’, 2.1% (n=7) mild-moderate’, and 1.2% (n=4) ‘moderate’ dysfunction. For verbal fluency (COWA), older BCS demonstrated significant dysfunction with 40.4% (n=135) ‘mild’18.6% (n=62) ‘mild-moderate’, and 7.5% (n=25) ‘moderate’ dysfunction [126].

Table 3-4 depicts the mean, standard deviation (SD), potential and actual score range, and the percentage of older BCS in each threshold for the subjective cognitive function using the Attention Function Index (AFI). Based on predetermined cut points, 26% (n=87) of BCS reported poor to moderate attention function and the majority 70.8% (n= 237) reported effective attention function [71].

Pearson bivariate correlations were used to examine relationships between objective and subjective cognitive function measures (aim 2a) with full results depicted in Table 3-5. In bivariate analysis, subjective attention measured by the Attentional Function Index (AFI) was significantly correlated with objective cognitive functioning on two objective measures included in this study. Objective attention (Digit Span- Forward) and executive function-working memory (Digit Span- Backward) significantly correlated with the subjective attention (AFI; $r=.15$, $p<0.01$; $r=.18$ $p<0.01$), respectively. Objective immediate memory (AVLT), delayed memory (AVLT), and verbal fluency (COWA) were not significantly correlated with subjective attention (AFI).

Separate multiple linear regression models were used to determine the relationships between independent variables of age, education, comorbidities, time since diagnosis, breast cancer stage, depressive symptoms, anxiety, fatigue, and sleep disturbance in relation to dependent variables of cognitive function including immediate and delayed memory, attention, executive function-working memory, verbal fluency, and

subjective attention. Table 3-6 displays the results of the regression analysis. The models for immediate memory [F(9,300)=2.59, adjusted r_2=.04, p<.01], delayed memory [F(9,300)=1.98, adjusted r_2=.03, p<.05], verbal fluency [F(9,300)=4.11, adjusted r_2=.08, p<.001], and subjective attention [F(9,291)=26.54, adjusted r_2=.43, p<.001] were statistically significant. Models with objective attention and executive function-working memory were not significant. Immediate Memory: The model explained 4% of the variance of immediate memory, with age (β=-0.14, p<.05) and depressive symptoms (β=-0.24, p<.01) related to immediate memory. These results indicated that higher scores, older age and more depressive symptoms, were negatively related to immediate memory. Delayed Memory: The model explained 3% of the variance of delayed memory, with depressive symptoms (β=-0.23, p<.01) related to delayed memory. These results indicated that higher scores, more depressive symptoms, was negatively related to delayed memory. Verbal Fluency: The model explained 8% of the variance of verbal fluency, with education (β=0.23, p<.01) and depressive symptoms (β=-0.24, p<.01) related to verbal fluency. These results indicated that higher scores, more education, was positively related to verbal fluency and higher scores, more depressive symptoms, were negatively related to verbal fluency. Subjective Attention: The model explained 43% of the variance of subjective attention, with education (β=0.10, p<.05), depressive symptoms (β=-0.24, p<.01), anxiety (β=-0.15, p<.05), and fatigue (β=0.39, p<.01) related to subjective attention. These results indicated that higher scores, more education and less fatigue, were positively related to subjective attention, and higher scores, more depressive symptoms and more anxiety, were negatively related to higher/better subjective attention.

Discussion

Older BCS are a growing population with unique needs. Many older BCS experience cognitive dysfunction, which has been previously understudied. This study helps to elucidate some of the complexity of cognitive dysfunction in older BCS by examining relationship between objective and subjective cognitive dysfunction and factors associated with both subjective and objective cognitive dysfunction, while also highlighting the prevalence of cognitive dysfunction in this population.

Older BCS in this study were noted to have clinically significant cognitive dysfunction on neuropsychological exam. Up to 18.6% of the older BCS demonstrated mild-moderate dysfunction (1.5 SD below the mean of NCCs) on at least one out of five neuropsychological assessments or cognitive domains. Immediate memory (AVLT) and verbal fluency (COWA) appeared to have the highest percentage of BCS with dysfunction. In addition, 26% (n=87) of older BCS reported moderate to poor subjective attention function (AFI) based upon published cut scores. The objective cognitive dysfunction results are similar to the literature [64]. In addition, subjective reports of poor to moderate dysfunction were somewhat higher than objective measures of dysfunction, which is also consistent with the larger BCS literature [103,104].

Both objective and subjective cognitive assessments are important tools for assessing cognition in BCS, although previous literature has shown that the instruments do not consistently correlate [113,123]. In this study, subjective attention (measured by the AFI) was modestly correlated with two objective cognitive domains, objective attention (measured by the Digit Span-forward) and executive function-working memory (measured by the Digit Span- backward). This work importantly identifies the AFI as a

sensitive measure for self-reported cognitive dysfunction, specifically for attention and executive function-working memory. The AFI is a short, 13-item, self-report instrument, which has potential use for practice, where it could be used as a brief screening tool for older BCS, identifying those with cognitive concerns [71]. The AFI could provide healthcare providers glimpse into potential concerns of older BCS regarding attention and executive function-working memory. The use of the AFI in clinic setting would be cost and time effective and is feasible as a quick assessment tool providing less disruption than a full neuropsychological assessment. Attention and executive function-working memory are important cognitive domains for older adult's independence and play a role in many daily activities such as driving, reading, and grocery shopping [127].

Although the models were not very explanatory regarding objective cognitive function (adjusted r_2 =.03-.08), there were some important and significant findings. Most notably, depressive symptoms (measured by the CES-D) were significantly related to both objective (immediate memory, delayed memory, and verbal fluency) and subjective cognitive dysfunction (attention) in this study of older BCS. This finding is important because unlike previous BCS studies, depressive symptoms and objective cognitive dysfunction have often not been correlated [34,39,41,98,128,129].

Depressive symptoms and cognitive dysfunction may significantly affect older BCS. Cognitive dysfunction can impede proper diagnosis and treatment or lead to underreporting of depressive symptoms in older adults [130]. In this sample, 16.8% (n=56) had depressive symptom scores ≥16, indicating clinically significant depressive symptoms [55,56,130]. Depressive symptoms may also affect cognitive functioning. In addition, depressive symptoms in older adults have been shown to be related to female

sex, cognitive dysfunction, and stressful life events [130]. Together these findings would indicate that older BCS may be a greater risk of both depressive symptoms and cognitive dysfunction [130]. This finding also highlights the importance of a comprehensive geriatric assessment in older BCS that includes the assessment of both depressive symptoms and cognitive dysfunction. Proper management of depression may also improve cognitive dysfunction; management of depressive symptoms part of the National Comprehensive Cancer Networks guidelines for cognitive dysfunction and important for clinical practice [33,42,130]. Overall, depressive symptoms are important, modifiable, amenable to treatment, and should not be overlooked in addressing the needs of older BCS.

Other cancer-related symptoms are also important factors associated with cognitive dysfunction. In this study, depressive symptoms (as previously mentioned), anxiety, and fatigue were related to subjective cognitive dysfunction (attention). In this study, sleep disturbance was not significant in the model, although other studies have found significance [43,97]. Similar results regarding the association of these cancer-related symptoms either as independent symptoms or as a psychoneurological symptom cluster have been noted in all age [131,129] and older BCS [23,24,39,43,100]. Tometich and colleagues (2019) examined the psychoneurological symptom cluster (depression, anxiety, fatigue, sleep disturbance and pain) and its relationship with cognitive functioning before systemic treatment, 12 months, and 24 months later in 319 older BCS. These researchers noted that older BCS with high levels of psychoneurological symptoms versus low psychoneurological symptoms was significantly related to greater objective and subjective cognitive dysfunction at baseline and 24 months later [43]. This work

supports a potential phenotype and is important for consideration in future research in older BCS. Research addressing predictors, mechanisms, management of this psychoneurological symptom cluster to improve QoL and functional impairment in older BCS is warranted [43].

Limitations

There are some limitations that should be noted in this study. This study is limited in that it used existing cross-sectional data that prohibited both employing other measures that may be related to cognitive dysfunction as well as limited interpretation of the data to association vs. causal inferences. However, this study provides a foundation to better understand the complex and unique issue of cognitive dysfunction in older BCS. The majority of the participants in this study were non-Hispanic white and very well-educated, which limits generalizability to the larger BCS population. In addition, only one aspect of subjective cognitive function was examined in this study, subjective attention measured by the AFI. Additional measures of subjective cognitive dysfunction could be useful when addressing the first aim examining the relationship between objective and subjective cognitive dysfunction. We ran multiple regression analyses with separate outcome variables increasing the risk for type I error; however, a power analysis was completed to ensure appropriate power. Overall, the model was not very explanatory; however, these findings do provide some insight into potentially important factors.

Conclusion

This study identifies cognitive dysfunction as a significant concern for older BCS 3-8 years post breast cancer diagnosis. The oldest BCS, with less education, and more depressive symptoms were most likely to have cognitive dysfunction. Finally, healthcare

providers should be aware of and assess for cognitive dysfunction in older BCS even years after diagnosis and treatment as it is clear cognitive dysfunction can still be a concern years after treatment as evident by the findings of this study.

Table 3-1 Sample Characteristics

Variable	**BCS (n=335) M (SD)**	**NCC (n=228) M (SD)**
Age at breast cancer diagnosis, years	63.85 (2.97)	n/a
Time since diagnosis, years	5.95 (1.48)	n/a
Age at data collection, years	69.79 (3.34)	64.21 (6.08)
Time duration initially treated for breast cancer, months	8.02 (4.12)	n/a
Education, years	13.73 (2.53)	15.34 (2.84)
	n (%)	**n (%)**
Race		
White	313 (93.4%)	183 (80.3%)
Non-white, Black, Asian, Multi-racial	22 (6.6%)	45 (19.7%)
Cancer stage at diagnosis		n/a
Stage I	67 (20%)	
Stage II	227 (67.7%)	
Stage III	33 (9.9%)	
Missing/No response	8 (2.4%)	
Surgery Type		n/a
Lumpectomy	157 (46.9%)	
Mastectomy	178 (53.1%)	
Radiation Therapy		n/a
Yes	203 (60.6%)	
No	121 (36.1%)	

Table 3-2 Cancer-Related Symptoms and Measures - Mean (SD), Potential Range, and Actual Range

Variable (Measure)	Mean (SD)	Potential Range	Actual Range
Depressive symptoms (CES-D)	8.73 (7.83)	0-60	0-41
Anxiety-State (STAI)	30.55 (9.56)	20-80	20-70
Fatigue (FACT-F)	41.28 (9.31)	0-52	5-52
Sleep Disturbance Subscale (PSQI)	1.33 (0.506)	0-3	0-3

CES-D = Center for Epidemiological Studies Scale; STAI = State-Trait Anxiety Inventory – State and Trait subscales; FACT-F = Functional Assessment of Cancer Therapy fatigue; PSQI = Pittsburgh Sleep Quality Index

Table 3-3 Objective Cognitive Measures and Dysfunction by Domain

Cognitive Domain (Measure)	**Mean (SD)**	**Potential Range**	**Actual Range**	**Dysfunction**		
				Mild 1 SD<NCC %	**Mild-Moderate** 1.5 SD<NCC %	**Moderate** 2 SD<NCC %
Older BCS (n=335)						
Immediate Memory (AVLT)	45.79 (8.96)	0-75	17-70	27.8%	12.9%	5.7%
Delayed Memory (AVLT)	9.12 (2.86)	0-15	1-15	19.2%	11.1%	3.3%
Attention (Digit Span-Forward)	10.1 (2.59)	0-16	5-16	4.2%	0%	0%
Executive function-working memory (Digit Span-Backwards)	7.48 (2.62)	0-14	1-14	9.9%	2.1%	1.2%
Verbal fluency (COWA)	34.74 (11.51)	N/A	10-76	40.4%	18.6%	7.5%
NCC Comparison Group (n=228)						
Immediate Memory (AVLT)	49.35 (9.06)	0-75	22-67	16.5%	7%	3%
Delayed Memory (AVLT)	10.09 (3.18)	0-15	0-15	15.5%	8.2%	2.1%
Attention (Digit Span-Forward)	8.34 (2.23)	0-16	2-13	23.3%	4.8%	1.4%

Cognitive Domain (Measure)	**Mean (SD)**	**Potential Range**	**Actual Range**	**Dysfunction**		
				Mild 1 SD<NCC %	**Mild-Moderate** 1.5 SD<NCC %	**Moderate** 2 SD<NCC %
Executive function-working memory (Digit Span-Backwards)	6.84 (2.11)	0-14	2-12	13.7%	4.8%	1.4%
Verbal fluency (COWA)	41.48 (11.06)	N/A	0-75	14.7%	6.1%	1.2%

AVLT=Rey Auditory Verbal Learning Test; COWA=Controlled Oral Word Association; SD=standard deviation; NCC=non-cancer control

Table 3-4 Subjective Attention Function Measure and Dysfunction

Variable (measure)	**Mean (SD)**	**Potential Range**	**Actual Range**	**Effective** (scores >75) N (%)	**Moderate** (scores 50-75) N (%)	**Poor** (scores <50) N (%)
Attention Function (AFI)	91.54 (21.7)	0-130	34-130	237 (70.8%)	77 (23%)	10 (3%)

AFI=Attentional Function Index; Missing=11 (3.2%)

Table 3-5 Cognitive Measure Bivariate Correlations

Variable (measure) (n=335)	**1**	**2**	**3**	**4**	**5**	**6**
1. Immediate memory (AVLT)	-					
2. Delayed memory (AVLT)	.693**	-				
3. Attention (Digit Span - Forward)	.299**	.238**	-			
4. Executive function - working memory (Digit Span - Backwards)	.294**	.281**	.676**	-		
5. Verbal fluency (COWA)	.240**	.147**	.177**	.110*	-	
6. Subjective attention (AFI)	.085	.651	.151**	.178**	.101	-

*p<.05; **p<.01; AVLT = Rey Auditory Verbal Learning Test; COWA = Controlled Oral Word Association; AFI = Attention Function Index

Table 3-6 Regression Analysis Summary for Demographic, Medical, and Treatment Factors, Cancer-Related Symptoms, and Cognitive Function Measures

	Immediate Memory	**Delayed Memory**	**Attention**	**Executive Function-Working Memory**	**Verbal Fluency**	**Subjective Attention**
Age	β=-.14*					
Education					β=.23**	β=.10*
Comorbidities						
Time Since Diagnosis						
Breast Cancer Stage						
Depressive Symptoms	β=-.24**	β=-.23**			β=-.24**	β=-.24**
Anxiety						β=-.15*
Fatigue						β=.39**
Sleep Disturbance						
F	2.59**	1.98*	.577	.739	4.11**	26.54**
R_2	.07	.06	.017	.022	.11	.45
Adjusted r_2	.04	.03	-.012	-.008	.08	.43

*p<.05; **p<.01

CHAPTER 4

Introduction

Comorbidities are common among older adults, the majority (80%) have at least one comorbid condition, with the most common comorbidities being cardiovascular disease, obesity, diabetes, and arthritis [132]. In addition, individuals who have had cancer tend to report more comorbidities than those with no history of cancer [133]. Cognitive dysfunction, a common cancer-related symptom experienced by breast cancer survivors (BCS), has been associated with comorbidities in the larger aging literature [134]. The relationship between comorbidities and cognitive dysfunction in older BCS specifically has begun to be addressed in the literature as well, although findings have been mixed [23,24,34,39,41,98,135]. With the high probability that older BCS will most likely also have other comorbid conditions, and the commonality of cognitive dysfunction among older BCS, this is an important area for further investigation.

Comorbidities and cognitive dysfunction have also been related to decreased levels of physical functioning [136] and decreased quality of life (QoL) in older adults [137,138]. Physical functioning is important to living well and is especially important for older adults and living independently [139]. Decreased physical functioning can lead to the need for hospitalization, long-term care, and premature death [139]. QoL is important to older adults, with health, including symptoms, and ability identified as most important [140]. In general, decreased or poor physical functioning and QoL and have far reaching implications and impact upon the lives of older adults in general. These relationships have begun to be investigated in older BCS; however, there is limited data and the studies

completed previously have focused on older BCS in treatment and up to 2 years post-treatment.

Therefore, the purpose of this study was to examine comorbidities, objective cognitive function, and subjective cognitive function and their relationship with physical functioning and QoL in older BCS 3-8 years post-diagnosis, controlling for age and education. This work is important for older BCS, their families, and caregivers as well as healthcare providers, including primary care providers or geriatricians who will be seeing older BCS and should be aware of these issues and their implications.

Methods

For this secondary data analysis study, cross-sectional data were leveraged from a BCS study aimed at examining QoL in younger versus older BCS (American Cancer Society RSGPB-04-089-01, PI: V. Champion) [52]. Full details regarding recruitment, eligibility criteria, and data collection can be found in chapters 1 and 3.

Population and Data Collection

This study focuses on older BCS who were 60 years of age and older, 3-8 years post-diagnosis for stage I-III breast cancer without recurrence and treated with chemotherapy. Eligible older BCS were recruited from one of the 97 Eastern Cooperative Oncology Group (ECOG) cites and Indiana University (IU). IRB approval was obtained by IU and all participating ECOG sites. Once verbal informed consent was obtained for interested BCS, written consents and questionnaires were mailed to BCS. Participants then set a date for their neuropsychological assessment, which was performed by trained staff via the telephone. Participants received $50 total for completing both the survey and the telephone neuropsychological assessment.

Measures

Demographic. Standard demographic data (i.e. age, race, ethnicity, marital status, education) were collected via an investigator-initiated self-report questionnaire.

Comorbidities. Comorbidities were collected via self-report survey where BCS responded yes or no to a list of potential comorbid conditions including: arthritis, heart disease or heart problem, high blood pressure or hypertension, stroke, serious breathing disease or problem, kidney disease or problem, high cholesterol, diabetes, leukemia or cancer (not breast cancer), anxiety/panic disorders, depression, eating disorders, hip fracture, surgical replacement of joint, problem with urinary control, eye problems (other than corrective lenses), hearing problems, Other problem – please specify, and none. For the analyses in this study the total number of comorbidities were reported.

Objective Cognitive Function. Objective cognitive function including immediate memory, delayed memory, attention, executive function-working memory, and verbal fluency were measured using valid and reliable neuropsychological assessments that have been used in BCS. The Rey Auditory-Verbal Learning Test (AVLT) was used to assess immediate and delayed memory by completing a 15-word learning task, where the tester lists 15 words and the participant must try to remember and recite them [63,65,66]. For both immediate and delayed memory, higher scores indicating better functioning [63,65,66]. The Wechsler Adult Intelligence Scale (WAIS) - Digit Span Forward and Backward were used to assess attention and executive function-working memory, respectively. For the Digit Span test, the tester lists numbers in a string and the participant must recite them in order for the Forward test and must recite the numbers in reverse order for the Backward test [67,68]. For both the Digit Span-Forward and

Backward, higher scores indicating better functioning [67,68]. The Benton Controlled Oral Word Association Test (COWA) was used to assess verbal fluency by giving the participant a letter and 1-minute to produce as many words as possible that begin with that letter (excluding proper nouns) [69,70,124]. Potential and actual score ranges for this test will vary, however higher scores indicating better functioning [69,70,124].

Subjective Cognitive Function. The Attentional Function Index (AFI) is a 13-item scale was used to assess subjective attention at the present time. Potential scores can range from 0-130, with higher scores indicate better functioning [71]. In this study, the AFI Cronbach alpha was .80 indicating good reliability.

Physical Functioning. The physical functioning (PF-10) is a subscale of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36). The PF-10 is 10-items and measures the participants perceived limitations of physical functioning during the past four weeks with higher scores indicating less limitation or disability [72]. The PF-10 is an established measure of physical functioning that has shown reliability and validity in various populations including cancer patients [72]. In this study, the Cronbach alpha was .89 indicating good reliability.

Quality of Life. The Index of Well-Being-Survivor (IWB) instrument measures overall QoL including life satisfaction and subjective well-being [74]. This is a 9-item measure developed to assess specific concerns of long-term cancer survivors with higher scores indicating higher/better QoL. The IWB scale has established reliability and validity and has been widely used in cancer patients including BCS [52,73]. In this study, the Cronbach alpha was .92 indicating good reliability.

Data Analysis

Descriptive statistics were computed to describe the sample and ensure data quality, identify out of range values, and evaluate the assumptions of statistical tests including normality and intercorrelation of independent variables. Separate multiple linear regression models were used to examine the relationships between the independent variables of age (years age at neuropsychological assessment), education (total number of years of education), comorbidities (total number of self-reported comorbidities), objective cognitive function (immediate memory, delayed memory, attention, executive function-working memory, and verbal fluency) and subjective cognitive function (attention) and dependent variables of physical functioning (PF-10) and QoL (IWB) in older BCS. Significance level was set at 0.05. SPSS statistical software, version 26 was used for all data analysis.

Results

Older BCS (n=335) who participated in this study were 3-8 years post-diagnosis (M 5.95, SD 1.48) and 60-70 years of age (M 63.85, SD 2.97). On average long-term older BCS reported having 3 (SD 1.81) comorbid conditions, with total number of comorbid conditions ranging from 0-12 throughout this sample. The most common comorbidities reported were hypertension (n=192; 57.3%), arthritis (n=186; 55.5%), and high cholesterol (n=151; 45.1%). Table 4-1 depicts a more thorough breakdown of comorbidities reported by long-term older BCS in this study. Chapter 3 gives greater detail on the sample characteristics of this study including education, race, marital status, income, and treatment factors (radiation, surgery).

Descriptive information about the outcome variables/measures of physical functioning and QoL including, mean, standard deviation, potential score range, and actual score range for this study can be found in Table 4-2. Actual physical functioning scores ranged from 5-100, with older BCS in this sample reporting scores of 70.71 (SD 22.94) on average. Actual QoL scores ranged from 8.85-14.7, with older BCS in this sample reporting scores of 10.03 (SD 2.31) on average. For both of these scales, higher scores indicate better functioning.

The regression analyses examining age, education, comorbidities, objective cognitive function and subjective cognitive function and their relationship with physical functioning and QoL in older BCS are displayed fully in Table 4-3 and described in detail below.

Physical Functioning

Immediate Memory: The model including age, education, comorbidities, and immediate memory was significant [$F(4,321)= 27.15$, adjusted $r_2=.24$; $p<.001$]. The model explained 24% of the variance of physical functioning, with education ($\beta=.12$, $p<.05$) and comorbidities ($\beta=-0.48$, $p<.001$) related to physical functioning. These results indicated that higher scores, more education, was positively related to physical function and more comorbidities was negatively related to physical function. Delayed Memory: The model including age, education, comorbidities, and delayed memory was significant [$F(4,321)= 26.95$, adjusted $r_2=.24$; $p<.001$]. The model explained 24% of the variance of physical functioning, with education ($\beta=.12$, $p<.05$) and comorbidities ($\beta=-0.48$, $p<.001$) related to physical functioning. These results indicated that higher scores, more education, was positively related to physical function and more comorbidities was

negatively related to physical function. Attention: The model including age, education, comorbidities, and attention was significant [F(4,321)= 26.76, adjusted r_2=.24; p<.001]. The model explained 24% of the variance of physical functioning, with education (β=.13, p<.05) and comorbidities (β=-0.48, p<.001) related to physical functioning. These results indicated that higher scores, more education, was positively related to physical function and more comorbidities was negatively related to physical function. Executive Function-Working Memory: The model including age, education, comorbidities, and executive function-working memory was significant [F(4,321)= 26.76, adjusted r_2=.24; p<.001]. The model explained 24% of the variance of physical functioning, with education (β=.13, p<.05) and comorbidities (β=-0.48, p<.001) related to physical functioning. These results indicated that higher scores, more education, was positively related to physical function and more comorbidities was negatively related to physical function. Verbal Fluency: The model including age, education, comorbidities, and verbal fluency was significant [F(4,321)= 26.76, adjusted r_2=.24; p<.001]. The model explained 24% of the variance of physical functioning, with education (β=.13, p<.05) and comorbidities (β=-0.48, p<.001) related to physical functioning. These results indicated that higher scores, more education, was positively related to physical function and more comorbidities was negatively related to physical function. Subjective Attention: The model including age, education, comorbidities, and subjective attention was significant [F(4,312)= 33.81, adjusted r_2=.29; p<.001]. The model explained 29% of the variance of physical functioning, with education (β=.11, p<.05), comorbidities (β=-0.42, p<.001), and subjective attention (β=.23, p<.001), related to physical functioning. These results indicated that higher scores, more education and better subjective attention, were

positively related to physical functioning and more comorbidities was negatively related to physical functioning.

Quality of Life

The regression analysis models for age, education, comorbidities and objective cognitive measures (immediate memory, delayed memory, attention, executive function-working memory, and verbal fluency) and QoL were not significant. However, the model for subjective attention was significant. Subjective Attention: The model including age, education, comorbidities, and subjective attention (AFI) related to QoL was significant [$F(4,310)= 12.59$, $R_2=.14$, adjusted $r_2=.13$; $p<.001$]. The model explained 13% of the variance of QoL, with subjective attention ($\beta=.39$, $p<.001$) significantly related to QoL. These results indicated that higher scores, better subjective attention, was positively related to QoL.

Discussion

Many older BCS experience multiple comorbidities as well as cognitive dysfunction following cancer diagnosis and treatment. Both of these can have negative consequences or implications for the older BCS, including decreased physical functioning and QoL, which in turn, hold their own negative implications. This study aids in illustrating some of the implications for physical functioning and QoL in older BCS by examining the associations between comorbidities and cognitive dysfunction with physical functioning and QoL.

The findings of this study highlight the relationship between comorbidity and physical functioning within the regression models. Interestingly, comorbidities were not related to QoL in any of the regression analysis models, which contrasts the aging and

cancer literature where comorbidities have been linked to QoL [137,138]. The most common comorbidities for the older breast cancer survivors in this study were similar to that of the general older adult population, hypertension and arthritis. Approximately 94% (n=314) of the older BCS in this study, had at least one comorbid condition, as compared to 80% reported on average in the general older adult population [132]. This validates that individuals who have had cancer are more likely to have comorbidities than those without a history of cancer diagnosis and treatment [133]. Increased comorbidities and decreased physical functioning can have serious consequences in older adults [139]. In addition, cardiovascular disease, a common comorbidity, has been identified as the leading cause for morbidity in older BCS [142]. These findings taken together highlight the importance of managing comorbid conditions by healthcare providers treating older BCS.

Subjective cognitive dysfunction (subjective attention), measured by the AFI in this study was significantly related in the model to physical functioning. In studies in older adults, subjective cognitive dysfunction has been shown to be correlated with subjective reports of physical functioning impairment. In a study regarding trajectories of subjective cognitive decline, Mandelblatt and colleagues (2016) found that accelerated cognitive decline was associated with a decline in physical functioning in older BCS [23]. However, unlike subjective cognitive function, objective measures of cognitive function were not specifically related to physical functioning in any of the models. Similar findings have been noted in previous studies in older BCS that have examined this relationship [34,39,41]. Lange et al. (2014) found that in 123 older BCS with a mean age of 70 years old, objective cognitive dysfunction was not related to performance status,

which they hypothesized was likely due to a large proportion of BCS being in very good general health [39]. More research is needed to fully understand the link between cognitive dysfunction and physical functioning in older BCS.

Subjective cognitive dysfunction (subjective attention), was also significantly related in the model to QoL. Importantly, this finding suggests that perceived or subjective cognitive dysfunction has implications to QoL. Similar findings have been noted in all age BCS [73] and older BCS [39,100]. However, objective measures of cognitive function were not related to QoL in any of the models. Often times objective measures of cognitive dysfunction do not correlate with subjective reports of QoL. Similarly, Biglia and colleagues (2012) found that objective cognitive dysfunction was not related to QoL in 40 all age BCS [128]. In contrast, Lange et al. (2016) found that objective cognitive decline was associated with the QoL subscale of the Functional Assessment of Cancer Therapy, Cognitive Scale (FACT-Cog) in 119 older BCS [34]. This relationship may be the result of asking specifically about QoL concerns related to cognitive dysfunction [34]. More research is needed to generate data on the relationship between cognitive dysfunction and QoL to fully understand the impact cognitive dysfunction has on QoL in older BCS and to begin to develop interventions to alleviate issues in older BCS.

Limitations

Although this study provides new information regarding comorbidity, cognitive functioning, physical functioning, and QoL in older BCS, the study does have limitations that should be addressed. The data for this study is cross-sectional in nature, providing a snapshot of the variables at one point in time, which limits the ability to determine casual

relationships. A prospective, longitudinal study may have provided more insight into how these relationships work. We ran multiple regression analyses with separate outcome variables increasing the risk for type I error; however, a power analysis was completed to ensure appropriate power. In addition, the majority of the older BCS in this study are white (93%), therefore all races are not represented in this study, which limits generalizability to the overall BCS population. Future studies should focus on recruiting more racially diverse samples.

Conclusion

Overall, older BCS with fewer years of education, more self-reported comorbidities, and worse subjective cognitive function had worse physical functioning. As for QoL, older BCS in this study who reported better subjective cognitive function reported better QoL. These findings are important when considering survivorship care for older BCS, including maintenance of physical functioning and QoL, which can impact independence, hospitalization, need for long-term care, and even mortality.

Table 4-1 Self-reported Comorbid Conditions

Average Number of Comorbid Conditions	**M (SD)** (n=335)
	3.06 (1.81)
Total Number of Comorbid Conditions	**% (n)**
0	6.3% (21)
1-2	31.9% (107)
3-4	39.4% (132)
≥5	22.4% (75)
Comorbid Condition	**% (n)**
High blood pressure or hypertension	57.3% (192)
Arthritis	55.5% (186)
High cholesterol	45.1% (151)
Eye problems (other than corrective lenses)	24.8% (83)
Depression	17.3% (58)
Diabetes	16.4% (55)
Heart disease or heart problem	14% (47)
Other	13.4% (45)
Surgical replacement of joint	12.8% (43)
Problem with urinary control	12.2% (41)
Anxiety/panic disorders	9.6% (32)
Serious breathing disease or problem	8.1% (27)
Hearing problems	6.9% (23)
Stroke	3.3% (11)
Leukemia or cancer (not breast cancer)	3.3% (11)
Kidney disease or problem	2.4% (14)
Eating disorders	1.2% (4)
Hip fracture	0.9% (3)

*(descending order from most prevalent to least prevalent condition)

Table 4-2 Outcome Variables and Measures - Mean (SD), Potential Range, and Actual Range

Variable (Measure)	**Mean (SD)**	**Potential Range**	**Actual Range**
Physical Functioning (PF-10)	70.71 (22.94)	0-100	5-100
QoL (IWB)	12.03 (2.31)	2.1-14.7	2.85-14.7

PF-10 = physical functioning 10 subscale; IWB = Index of Well-Being

Table 4-3 Regression Analysis Summary for Age, Education, Comorbidities, Cognitive Function Measures, Physical Functioning, and Quality of Life

Immediate Memory		
	Physical Functioning (PF-10)	**QoL** (IWB)
Age (age at data collection)		
Education (number of years)	β=.12*	
Comorbidities (self-reported total number of comorbid conditions)	β=-.48**	
Immediate Memory (AVLT)		
F	27.15**	.61
R_2	.25	.01
Adjusted r_2	.24	-.01
Delayed Memory		
	Physical Functioning (PF-10)	**QoL** (IWB)
Age (age at data collection)		
Education (number of years)	β=.12*	
Comorbidities (self-reported total number of comorbid conditions)	β=-.48**	
Delayed Memory (AVLT)		
F	26.95**	.67
R_2	.25	.01
Adjusted r_2	.24	.00
Attention		
	Physical Functioning (PF-10)	**QoL** (IWB)
Age (age at data collection)		
Education (number of years)	β=.13*	
Comorbidities (self-reported total number of comorbid conditions)	β=-.48**	

Attention (Digit Span-Forward)		
F	26.76**	1.19
R_2	.25	.02
Adjusted r_2	.24	.00
Executive Function-Working Memory		
	Physical Functioning (PF-10)	**QoL** (IWB)
Age (age at data collection)		
Education (number of years)	β=.13*	
Comorbidities (self-reported total number of comorbid conditions)	β=-.48**	
Executive Function-Working Memory (Digit Span-Backward)		β=.11*
F	26.76**	1.52
R_2	.25	.02
Adjusted r_2	.24	.01
Verbal Fluency		
	Physical Functioning (PF-10)	**QoL** (IWB)
Age (age at data collection)		
Education (number of years)	β=.13*	
Comorbidities (self-reported total number of comorbid conditions)	β=-.48**	
Verbal Fluency (COWA)		
F	26.76**	.70
R_2	.25	.01
Adjusted r_2	.24	.00
Subjective Attention		
	Physical Functioning (PF-10)	**QoL** (IWB)
Age (age at data collection)		

Education (number of years)	β=.11*	
Comorbidities (self-reported total number of comorbid conditions)	β=-.42**	
Subjective Attention (AFI)	β=.23**	β=.39**
F	33.81**	12.59**
R_2	.30	.14
Adjusted r_2	.29	.13

*p<.05; **p<.01; PF-10=Physical functioning – 10 sub-scale; IWB=index of well-being; AVLT=Rey Auditory Verbal Learning test; COWA=Controlled Oral Word Association test; AFI=Attention Function Index

CHAPTER 5

Introduction

The purpose of this dissertation study was to add to the literature and body of knowledge regarding cognitive dysfunction in older breast cancer survivors (BCS) and to fully characterize cognitive dysfunction in older BCS. Chapter 1 was an introduction, highlighting the background, significance, and conceptual framework that laid the foundation for the subsequent chapters. Chapter 2 described an integrative review of 12 studies previously published regarding cognitive dysfunction in older BCS. Information from that review provided additional background and support for the following chapters. Chapter 3 and 4 described the quantitative descriptive studies, which leveraged previously collected cross-sectional data to examine relationships. Chapter 3 specifically examined the relationships between objective cognitive function and subjective cognitive function, and the relationships between demographic factors, medical factors, treatment factors, and cancer-related symptoms and objective and subjective cognitive function, in older BCS. Chapter 4 examined the relationships between comorbidities, objective cognitive function, and subjective cognitive function and physical functioning and quality of life (QoL), in older BCS. The present chapter will summarize the key dissertation findings, describe and address the strengths and limitations of the dissertation study, and provide implications for future research and practice regarding cognitive dysfunction in older BCS.

Summary of Key Findings

Chapter 2

The purpose of chapter 2 was to identify and synthesize the current evidence regarding cognitive dysfunction in older BCS, including the prevalence and factors associated with objective and subjective cognitive dysfunction. The purpose was addressed by completing an integrative review using the Whittemore and Knafl method [76]. Twelve studies, which focused on cognitive dysfunction in older BCS, were included in the review. Cognitive dysfunction among older BCS was common both prior to and following treatment, although most of the studies did not extend beyond 2 years into survivorship. Older BCS experienced cognitive dysfunction as measured by both objective neuropsychological assessments and subjective (self-report) instruments. In addition, approximately half of the older BCS experienced cognitive decline from pre-to post-treatment regardless of the cognitive measure employed. The domains most impacted were memory, executive function, and processing speed. Throughout the studies in the review, both objective and subjective cognitive dysfunction was associated with age, comorbidities, chemotherapy receipt, sleep, psychoneurological symptom cluster, frailty, and QoL. Many of the factors associated with cognitive dysfunction are specific to the aging population and/or can be compounded in the aging population and could be detrimental to QoL and independent living. This integrative review identified gaps in the current literature about cognitive dysfunction in older BCS and provided a basis for the consecutive chapters.

Chapter 3

The purpose of chapter 3 was to examine the relationships between subjective and objective cognitive function and factors associated with both subjective and objective cognitive function in older BCS, to address this gap in the literature identified in chapter 2. The purpose was addressed by a cross-sectional descriptive study, which leveraged previously collected data from older BCS (n=335). Cognitive dysfunction was prevalent with up to 18.6% of older BCS experiencing mild-moderate dysfunction (1.5 standard deviations below the mean of non-cancer controls) in at least one cognitive domain. Poor to moderate subjective attention function was reported by 26% of older BCS in this sample. Pearson bivariate correlations were used to examine relationships between objective and subjective cognitive function measures. Subjective attention measured by the Attentional Function Index (AFI) was significantly correlated with objective cognitive functioning on two measures, objective attention (Digit Span- Forward) and executive function-working memory (Digit Span- Backward) ($p<0.01$). Separate linear regression models were used to determine the relationships between independent variables of demographic factors (age and education), medical factors (comorbidities), and treatment factors (time since diagnosis and breast cancer stage), and cancer-related symptoms (depressive symptoms, anxiety, fatigue, and sleep disturbance) in relation to dependent variables of cognitive function including immediate memory, delayed memory, attention, executive function-working memory, verbal fluency, and subjective attention. Although the models were not very explanatory, the models for immediate memory ($p<.01$), delayed memory ($p<.05$), verbal fluency ($p<.001$), and subjective attention ($p<.001$) were statistically significant; whereas, objective attention and

executive function-working memory were not significant. Across all of the significant models depressive symptoms was most notable and was significantly related to both objective and subjective cognitive functioning. In addition, age, education, anxiety and fatigue also were significant. These findings indicate that depression in older BCS is an exceedingly important factor related to cognitive functioning and should be acknowledged in future research and care for older BCS.

Chapter 4

The purpose of chapter 4 was to examine comorbidities, objective cognitive function, and subjective cognitive function and their relationship with physical functioning and QoL in older BCS, controlling for age and education. The purpose was addressed by utilizing cross-sectional data previously collected data from older BCS (n=335). Separate linear regression models were used to examine the relationships. All of the models for physical functioning were significant with less education, more comorbidities, and worse subjective attention being related to decreased physical functioning, objective cognitive function was not significant in the models. One model was significant for QoL, with only worse subjective attention being related to worse QoL. Overall, in this chapter, increased number of self-reported comorbidities and poorer subjective attention function were most important and should be incorporated in future research and practice when investigating or assessing for issues regarding physical functioning and QoL.

Strengths and Limitations

There are many strengths of this dissertation. Multiple research priorities are addressed, including a focus on symptom science from the National Institute of Nursing

Research's (2017) strategic plan [44]. Additionally, this study addresses aging, cancer, and cognition which has been identified as a priority by the Cancer and Aging Research Group, the International Cancer and Cognition Task Force, the National Institute on Aging, the National Cancer Institute, and the Oncology Nursing Society [45-47]. A thorough examination of the current literature provided the background in which to base the dissertation study. The requisite foundation to characterize cognitive dysfunction in older BCS, and ultimately support evidence-based intervention development to mitigate cognitive dysfunction is provided in the findings. This study was innovative and unique as it leveraged a large, nationwide, underserved, and growing population of older (60 years of age and older) BCS who are 3-8 years post diagnosis, who have been historically excluded from most research. Most previous research regarding cognitive dysfunction in older BCS has been limited to up to 2 years post-treatment. In addition, both objective and subjective measures of cognitive function were used and the relationship between these measures was examined, which is needed in older BCS. Overall, this research advances the science and is a first step toward identifying those at greatest risk for cognitive dysfunction among older BCS.

There are several limitations to this study that must be considered. The cross-sectional data limits data analysis to association and no causal relationships can be made. We ran multiple regression analyses with separate outcome variables increasing the risk for type I error; however, a power analysis was completed to ensure appropriate power. The majority of the participants in this study were non-Hispanic white and mostly well-educated, which is not representative of the overall older BCS population. In addition, in using already collected data, other associated factors or potential consequences for this

analyses that may be of interest in this older BCS population (i.e. independent activities of daily living, frailty, objective measures of physical functioning, etc.) were not able to be explored. However, this study is an important step in understanding the complex problem of cognitive dysfunction in older BCS, addresses gaps in the current knowledge, and significantly adds to the body of literature.

Implications

This dissertation advances the knowledge regarding cognitive dysfunction in older BCS. Findings from this dissertation present implications for both research and practice. Future research must focus on better understanding the intersection between depression and cognitive dysfunction (performance and self-report) in older BCS specifically. In addition, older adults with a history of cancer often have multiple comorbidities. In this study, increased number of comorbidities was related to decreased physical functioning in older BCS, which also warrants further research. Subjective cognitive dysfunction (attention) was related to multiple other cancer-related symptoms (depressive symptoms, anxiety, and fatigue), as well as, physical functioning and QoL. Subjective attention could be an indicator of problems that could limit functional ability and well-being in older BCS, with negative implications that could lead to other untoward outcomes such as hospitalization, need for long-term care, and potentially even morbidity and mortality [139]. More research regarding the intersection of aging, cancer, comorbidities and cognitive dysfunction is needed for this growing population of older BCS. In addition, future research should move beyond characterizing cognitive dysfunction and focus on evidence-based interventions for cognitive dysfunction incorporating the unique needs of older BCS.

This topic and dissertation study also unearthed implications for practice regarding the assessment and care of older BCS and cognitive dysfunction. Although further study is needed, one important finding is the relationship between objective measures of attention and executive function-working memory and subjective attention. The AFI may be a valuable tool to screen or initially assess for cognitive dysfunction in older BCS. The AFI is a brief tool that could be administered by healthcare providers in a clinic setting and assist clinicians in identifying patients, which may require follow-up neuropsychological assessment. In addition, assessment, surveillance, and management of multiple comorbid conditions, especially depression, in older BCS is of particular importance for survivorship care and primary care of older adults who have a history of cancer. As noted, in this study depression may have ramifications related to cognitive dysfunction. Depression may be amenable to standardized treatment and if treated effectively could also potentially ameliorate cognitive dysfunction in older BCS [33]. In addition, the total number of comorbid conditions was related to physical functioning and is another area for clinicians to direct close attention. A thorough geriatric assessment should be a key component of the cancer care continuum for older BCS [81,82,118]. Cognitive dysfunction before, during, and after breast cancer diagnosis and treatment should be a target for assessment and treatment for healthcare providers, especially in older BCS.

Conclusions

Cognitive dysfunction is a common concern among older BCS. Findings from this study are important and can contribute to effective symptom management of older BCS as the results deepen the understanding of cognitive dysfunction in older BCS. This is an

important descriptive study and foundational knowledge for being able to design interventions to alleviate or mitigate cognitive dysfunction and its negative consequences in older BCS.

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CURRICULUM VITAE

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Education

Doctor of Philosophy — September 2020
Indiana University, Indianapolis, IN
Major: Nursing
Minor: Individualized-Interdisciplinary Gerontology

Bachelor of Science — August 2014
Indiana University, Indianapolis, IN
Major: Nursing
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Professional Experience

Predoctoral Fellow, Interdisciplinary Training in Biobehavioral Oncology (T32CA117865) — 2018-2020
Indiana University- Purdue University Indianapolis

Neuropsychological Tester — 2017-2020
Indiana University School of Nursing

Predoctoral Fellow, Training Grant in Health Behaviors Research (T32NR007066) — 2018-2020
Indiana University- Purdue University Indianapolis

Research Project Manager — 2014-2017
Indiana University School of Nursing

Research Assistant — 2013-2015
Indiana University School of Nursing

Patient Care Intern — 2013-2014
Indiana University Health

Certifications and Licensure

Registered Nurse (expires 10/31/2021)
Indiana State Board of Nursing

Academic and Professional Honors

Indiana University School of Nursing Alumni Association
Emily Holmquist Award — 2019
Indiana University-Purdue University Indianapolis

Jonas Scholar — 2018-2020
Jonas Nursing and Veterans Healthcare

Elite 50 Graduate Student Award — 2017
Indiana University-Purdue University Indianapolis

Publications

Crouch, A., Champion, V. & Von Ah, D. (2020; under review). Cognitive dysfunction in older breast cancer survivors: An integrative review. Cancer Nursing.

Von Ah, D., & Crouch, A. (2020). Cognitive rehabilitation for cognitive dysfunction after cancer and cancer treatment: Implications for nursing practice. Seminars in Oncology Nursing, 36(1), 150977.

Crouch, A., & Von Ah, D. (2018). Incidence and factors associated with attentional fatigue in working long-term breast cancer survivors. Clinical Nurse Specialist: The Journal for Advanced Nursing Practice, 32(4), 177-181.

Von Ah, D., Storey, S., & Crouch, A. (2018). Relationship between self-reported cognitive function and work-related outcomes in breast cancer survivors. Journal of Cancer Survivorship, 12(2), 246-255.

Von Ah, D., Storey, S., Crouch, A., Johns, S. A., Dodson, J., & Dutkevitch, S. (2017). Relationship of self-reported attentional fatigue to perceived work ability in breast cancer survivors. Cancer Nursing, 40(6), 464-470.

Crouch, A., Von Ah, D., & Storey, S. (2017). Addressing cognitive impairment after breast cancer: What do women want?. Clinical Nurse Specialist: The Journal for Advanced Nursing Practice, 31(2), 82-88.

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Von Ah, D., Spath, M., Nielsen, A., & Fife, B. (2016). The caregiver's role across the bone marrow transplantation trajectory. Cancer Nursing, 39, E12-9.

Presentations

(*Paper, †Poster Discussion, #Poster, §Symposium)

Crouch, A. & Von Ah, D. (2020). Prevalence of cognitive dysfunction in older long-term breast cancer survivors. Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO). (Conference canceled).

Von Ah, D. & Crouch, A. (2020). Everyday cognitive function and work engagement in breast cancer survivors. Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO). (Conference canceled).

Crouch, A. & Von Ah, D. (2020). Cognitive rehabilitation for cognitive dysfunction after cancer and cancer treatment: Implications for nursing practice. Midwest Nursing Research Society 44th Annual Research Conference, April 1-4. (Virtual conference).

† Von Ah, D. & Crouch, A. (2020). Relationship of perceived everyday cognitive function and work engagement in breast cancer survivors. Midwest Nursing Research Society 44th Annual Research Conference, April 1-4. (Virtual conference).

Crouch, A. & Von Ah, D. (2020). Relationship between hypertension and memory in breast cancer survivors. 7th Biennial International Cancer and Cognition Taskforce (ICCTF) Meeting. Denver, CO, February 3-4.

Crouch, A., Ofner, S., & Von Ah, D. (2019). The association between self-reported cognitive abilities and commonly reported symptoms in long-term breast cancer

survivors. Sigma Theta Tau International Nursing Research Congress, Rising Stars of Research and Scholarship Poster. Calgary, Alberta, Canada July 25-29.

Crouch, A., Ofner, S., & Von Ah, D. (2019). The relationship between subjective cognitive ability and anxiety, depressive symptoms, and fatigue in breast cancer survivors. Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO), San Francisco, CA, June 21-23.

Crouch, A., Ofner, S., & Von Ah, D. (2019). The association between self-reported cognitive abilities and commonly reported symptoms in long-term breast cancer survivors. Indiana University Simon Cancer Center (IUSCC) Cancer Research Day, Indianapolis, IN, May 15. (2nd place among behavioral and population science graduate students)

Crouch, A. & Von Ah, D. (2018). Cognitive impairment in older breast cancer survivors: A comprehensive review of the literature. Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO), Vienna, Austria, June 28-30.

Von Ah, D. & Crouch, A. (2018). Perceived cognitive function: Its impact on work in breast cancer survivors. Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO), Vienna, Austria, June 28-30.

Von Ah, D., Champion, V., Monahan, P., Stump, T., Crouch, A., Cella, D., Unverzagt, F. (2018). Association of cognitive impairment and quality of life in breast cancer survivors. Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO), Vienna, Austria, June 28-30.

Crouch, A., & Von Ah, D. (2018). Cognitive impairment in older breast cancer survivors: An integrative review. Midwest Nursing Research Society 42nd Annual Research Conference, Cleveland, OH, April 12-15.

Von Ah, D., Champion, V., Monahan, P., Stump, T., Crouch, A., Cella, D., & Unverzagt, F. (2018). Cognitive impairment and quality of life in breast cancer survivors. Midwest Nursing Research Society 42nd Annual Research Conference, Cleveland, OH, April 12-15.

Dodson, J., Howard, C., Storey, S., Crouch, A., Dutkevitch, S., & Von Ah, D. (2017). Impact of perceived cognitive impairment on work-related outcomes in breast cancer survivors, 8th Annual Academy of Oncology Nurse & Patient Navigators Conference, Orlando, FL, November 17.

Crouch, A., Storey, S., & Von Ah, D. (2017). The significance of sleep disturbance and attentional fatigue among breast cancer survivors. Sigma Theta Tau International 44th Biennial Convention – Rising Stars of Research and Scholarship Poster, Indianapolis, IN, October 28 - November 1.

Dutkevitch, S., Crouch, A., Dodson, J., Howard, C., Storey, S., & Von Ah, D. (2017). Relationship between attentional fatigue and perceived work ability in breast cancer survivors. Central Indiana Oncology Nursing Society (CIONS) Enhance Your Passion, Profession, and Purpose Workshop, Indianapolis, IN, August 25, 2017.

Crouch, A., Storey, S., & Von Ah, D. (2017). Addressing cognitive impairment after breast cancer: What do women want? 42nd Annual Oncology Nursing Society Congress, Denver, CO, May 4-7.

* Von Ah, D., Storey, S., & Crouch, A. (2017). Impact of perceived cognitive impairment on work-related outcomes in breast cancer survivors. Oncology Nursing Society, Denver, CO, May 4-7. (One of Top Scored Abstracts and Labeled, "Best of ONS Oral Abstracts" and selected for podium presentation)

Crouch, A. (fka Nielsen), Storey, S., & Von Ah, D. (2017). Impact of sleep disturbance on attentional fatigue in breast cancer survivors. 41st Annual Midwest Nursing Research Society Conference, Minneapolis, MN, April 6-9.

§ Dodson, J., Von Ah, D., Nielsen, A., Dutkevitch, S., Howard, C., & Storey, S. (2016). Impact of attentional fatigue on perceived work ability in breast cancer survivors. 32nd Annual Association of Oncology Social Work Conference, Tampa, FL, May 4-6.

Dutkevitch, S., Nielsen, A., Dodson, J., Howard, C., Storey, S., & Von Ah, D. (2016). Relationship between attentional fatigue and perceived work ability in breast cancer survivors. 41st Annual Oncology Nursing Society Congress, San Antonio, TX, April 28 - May 1.

Von Ah, D., Nielsen, A., Storey, S., & Johns, S. (2016). Impact of attentional fatigue on perceived work ability in breast cancer survivors. 5th Biennial International Cognition and Cancer Taskforce (ICCTF) Meeting, Amsterdam, Netherlands, March 13-16.

Von Ah, D., Nielsen, A., Dutkevitch, S., Dodson, J., Howard, C. & Storey, S. (2015). Impact of attentional fatigue on perceived work ability in breast cancer survivors. Indiana University Health Research Days, Carmel, Avon, & Fishers, IN, November 17 & 20, and December 14.

Nielsen, A., Guilkey, R., Storey, S., Tang, C., & Von Ah, D. (2015). Physical activity level and symptoms after diagnosis and treatment for breast cancer. 39th Annual Midwest Nursing Research Conference, Indianapolis, IN, April 16-19.

Tang, C., Guilkey, R., Storey, S., Nielsen, A. & Von Ah, D. (2015). Impact of depressive symptoms and fatigue on quality of life in breast cancer survivors. 39th Annual Midwest Nursing Research Conference, Indianapolis, IN, April 16-19.

Guilkey, R., Storey, S., Tang, C., Nielsen, A., & Von Ah, D. (2015). Pain and anxiety and quality of life in breast cancer survivors. 39th Annual Midwest Nursing Research Conference, Indianapolis, IN, April 16-19.

Nielsen, A., Von Ah, D., Spath, M., Fife, B. (2014). The family caregiver's journey through bone marrow transplantation. 38th Annual Midwest Nursing Research Conference, St. Louis, Missouri, March 27-30.

* Nielsen, A., Von Ah, D., Spath, M., Fife, B. (2013). The family caregiver's journey through bone marrow transplantation. 39th Annual Nursing Research Conference, Indiana University Health, Indianapolis, IN, December 5. (Only student selected for podium presentation)